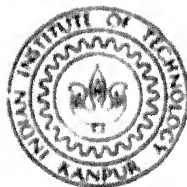


THE  
CHEMISTRY OF CHALCONES  
AND  
RELATED COMPOUNDS

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DEDICATED      TO      THE  
MEMORY      OF  
SIR      ROBERT      ROBINSON



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## FOREWORD

The chemical literature has grown enormously since the last war. It becomes increasingly difficult to read meaningfully what is published. Fortunately, the literature of Organic Chemistry is presented in internationally readable structural formulae. It is, as a consequence, far easier to find what is novel in the literature of Organic Chemistry than it is in the literature of (say) Biochemistry. Nevertheless, the physical burden of reading all the world's literature in Organic Chemistry as it becomes available is becoming a herculean task. Even if one works sixteen hours a day one would still not manage to read carefully all that is published.

One solution to this problem, that is increasingly adopted is not to bother to read the literature at all. One then relies on review articles, on attendance at meetings, on osmosis from one's friends and neighbours and on specialised monographs, for keeping oneself up to date.

This book by Dr. D.N. Dhar is a good example of a valuable specialised monograph. It deals in detail with the chemistry of chalcones and includes sections on physical properties and on biological activities.

However, a book like this is not only a pleasure to read as an authoritative treatise on an important subject, it also serves as a valuable reference book.

Dr. Dhar deserves the heartfelt thanks of the International Community of Organic Chemists for making available this splendid and up to date monograph. It will serve a very useful purpose.

Gif-sur-Yvette, France  
August 19, 1980

Sir Derek Barton

## PREFACE

The chemistry of chalcone has been recognized as a significant field of study. The phenomenal growth of publications in this area is undoubtedly a reflection of the interest it is receiving throughout the world. Unfortunately no book has appeared to date dealing exclusively with the broad aspects of chalcone chemistry. It was, therefore, felt that there exists a need for such a book which not only gives a background information about chalcones, but also provides a bird's eye view of the entire field. The work has been extended to include some derivatives of chalcones. The literature appearing in major journals and chemical abstracts has been covered through 1979. /

The general arrangement of the book is as follows : It is divided into four parts, comprising 19 chapters. Part I (Chapters 1-3) deals with an introduction to the subject and highlights the various methods of synthesis of substituted chalcones and includes some of the naturally occurring chalcones, viz., carthamin, sophoradin etc. Part II comprises six chapters (Chapters 4-9) which are essentially concerned with the various reactions of chalcones, for example, their reactions with oxidizing and reducing agents, ketones, esters, amides, cyanides, amines, organo-metallics, halogens etc. This includes cyclisation (chemical as well as biochemical), photochemical and polarographic

reactions. The physical properties of chalcones, including spectroscopic, X-ray crystallographic and dipole moment measurement studies form the subject matter of part III (Chapters 10-15) of the book. The colour reaction detection and estimation of chalcones are dealt with in Chapter 12, while the chromatographic methods of separation of chalcones from other flavonoids are described in Chapter 15. A list of naturally occurring chalcones, with some of their derivatives, is given in Chapter 16. Some of the chalcones are reported to inhibit the growth of several pathogenic microorganisms, fungi and are also claimed to exhibit some interesting therapeutic properties, viz., hypotensive and antipeptic ulcer activities (Chapter 17). Some of the chalcones and their derivatives find applications or are being considered for potential use, and these are covered in Chapter 19 (Part IV) of this book. Examples of these applications are the artificial sweeteners, stabilizers against heat, light and ageing of several materials, analytical reagents, scintillators polymerisation catalysts, preparation of photoconducting compositions etc. Chapter 18 is devoted in particular, to the reactions of two important derivatives of chalcones, viz., epoxides and  $\alpha, \beta$ -dibromides. These compounds serve as useful starting materials for the preparations of a large variety of related compounds. Comprehensive subject and author indexes arranged alphabetically, are

appended towards the end of the book.

It is my privilege to thank Prof. Sir Derek Barton, D.Sc., F.R.S., Nobel Laureate, for kindly contributing the Foreword to this book.

The writing of the concluding chapters of this book was done during an enjoyable visit to Shemyakin Institute of Bio-organic Chemistry U.S.S.R Academy of Sciences, Moscow, and I take this opportunity to thank Academicians Yu.A. Ovchinnikov and I.V. Torgov for their generous hospitality.

It is indeed a pleasure to acknowledge the assistance of my students, viz., Drs. A.K. Banerjee, S.C. Suri, A.K. Singh, P. Dwivedi, M/S. H.C. Misra, R. Raghunathan and K.S. K<sup>e</sup>shavamurthi who by their enthusiastic cooperation and generous donation of time and effort helped to make the book a reality. My thanks are due to Dr. S.S. Misra who undertook the arduous task of assisting me in literature survey. It is also a pleasure to record my appreciation to M/S. A.C. Saha, Anil Kumar and Bishember Nath for their continued cooperation.

I wish to thank the Educational Development Centre as well as the Curriculum Development Centre (Quality Improvement Programme) I.I.T. Kanpur for providing the financial assistance for preparation of the manuscript.

Finally, I wish to express my gratitude to my wife, Rupa, and my children, Preeti and Pankaj, for their understanding and patience during the period the work was in progress.

Kanpur, INDIA

Durga Nath Dhar

May 15, 1980



CONTENTSPART-I

<u>Chapter</u>		<u>Page</u>
1.	Introduction.....	1
2.	Synthetic Methods.....	6
3.	Some Classes of Chalcones and Chalcone Analogues..	33

PART-II

## Reactions of Chalcone with

4.1	reducing agents.....	50
4.2	Oxidising agents.....	68
4.3	Ketones.....	81
4.4	Esters.....	91
4.5	Amides.....	101
4.6	Cyanides, Isocyanides & Isocyanates.....	106
4.7	Amines.....	111
4.8	Organometallic Compounds.....	119
4.9	Halogens, Pseudo-halogens & Interhalogen Compounds.....	128
5.	Cyclisation Reactions of Substituted Chalcones....	134
6.	Biochemical Cyclisation and Degradation of Chalcones.....	151
7.	Miscellaneous Reactions of Chalcones.....	156
8.	Photochemistry of Chalcones and their Derivatives.....	194
9.	Polarographic Studies of Chalcones, Chalcone Analogues and their Derivatives.....	200

PART-III

10.	Properties of Chalcones and their Heterocyclic Analogues.....	211
11.	Complexing Action of Chalcones and their Derivatives.....	224
12.	Colour Reactions, Detection and Estimation of Chalcones.....	229
13.1	Stereoisomerism in Chalcones and their Derivatives.....	237
13.2	Stereochemistry of Chalcones and Chalcone Analogues.....	246
14.	Spectroscopic Studies of Chalcones and their Derivatives.....	260
15.	Chromatographic Separation of Chalcones from other Flavonoids.....	280

PART-IV

16.	Naturally Occurring Chalcones and their Derivatives.....	286
17.	Biologically Active Chalcones and their Derivatives.....	306
18.1	Chalcone Epoxides.....	344
18.2	Chalcone $\alpha$ , $\beta$ -Dibromides.....	361
19.	Uses.....	377
	Author Index.....	389
	Subject Index.....	431



ABBREVIATIONS

Ac	Acetyl	DNPH	Dinitrophenylhydrazine
Alc	Alcoholic	EDTA	Ethylenediaminetetraacetic acid
Aq	Aqueous	Et	Ethyl
Ar	Aryl	Liq	Liquid
B	Base	LAH	Lithium Aluminium hydride
Bz	Benzoyl	LCP	Lithium Chloropalladite
NBS	N-Bromosuccinimide	Me	Methyl
Bu	Butyl	NDA	N,N-Dimethylaniline
Conc	Concentrated	Nu	Nucleophile
DME	Dimethoxyethane	Ph, Ø	Phenyl
DMAD	Dimethylacetylene-dicarboxylate	PPA	Polyphosphoric acid
DMC	N,N-Dimethylchalcone	Py	Pyridine
DMF	Dimethylformamide	Satd	Saturated
DMSO	Dimethylsulphoxide	TN	Thallic nitrate
MSOM	Dimethylsulphoxonium methylide	Ts	Tosylate

PART - I

CHAPTER - 1

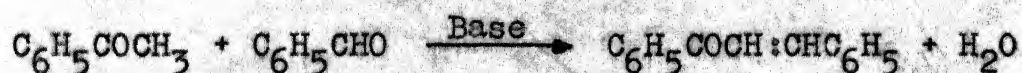
Introduction.....	1
Claisen-Schmidt Reaction.....	1
Mechanism of Chalcone Formation.....	2
Nomenclature.....	4
References.....	4

INTRODUCTION

Benzylideneacetophenones constitute a class of naturally occurring pigments which are oftentimes referred to as 'Chalcones'. The term was first coined by Kostanecki<sup>1</sup>, who did pioneering work in the synthesis of natural coloring compounds. An interesting feature of chalcones (polyhydroxylated) is that these serve as starting materials for the synthesis of another class of naturally occurring and widely distributed pigments called flavones.

CLAISEN-SCHMIDT REACTION

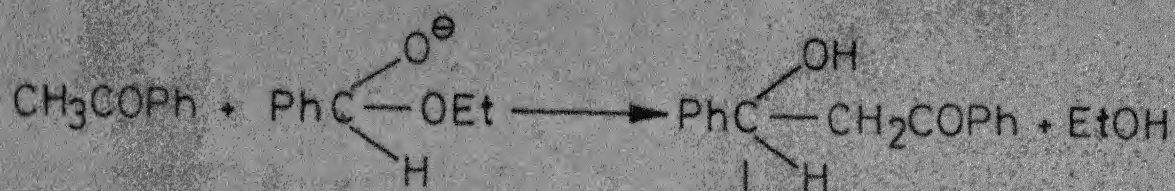
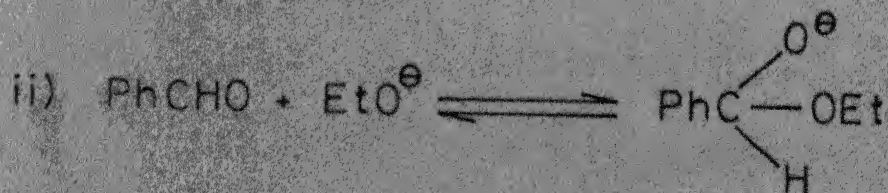
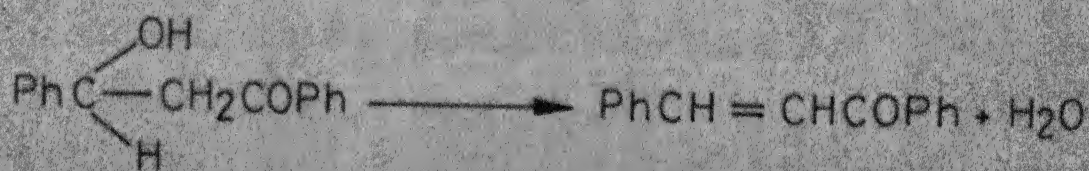
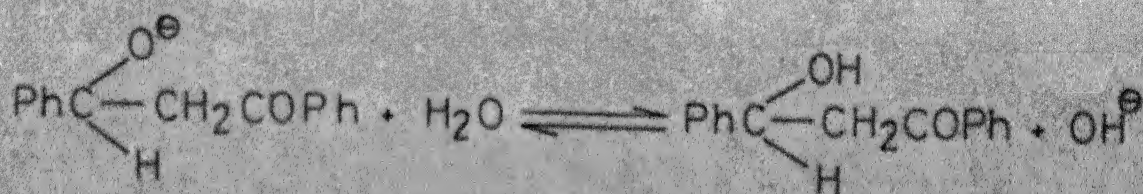
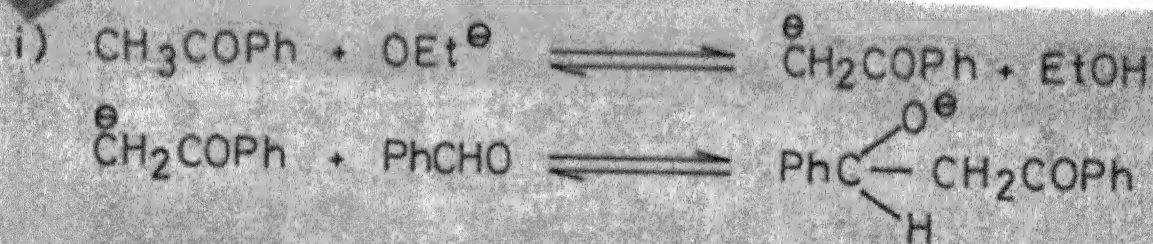
The synthesis of chalcone, the parent member of the series, has been accomplished in a variety of ways but perhaps the simplest method is the one involving the Claisen-Schmidt reaction. It consists in the reaction of acetophenone with benzaldehyde, in the presence of aqueous alkali or sodium ethylate, resulting in the formation of  $\alpha, \beta$ -unsaturated ketone<sup>2</sup>:



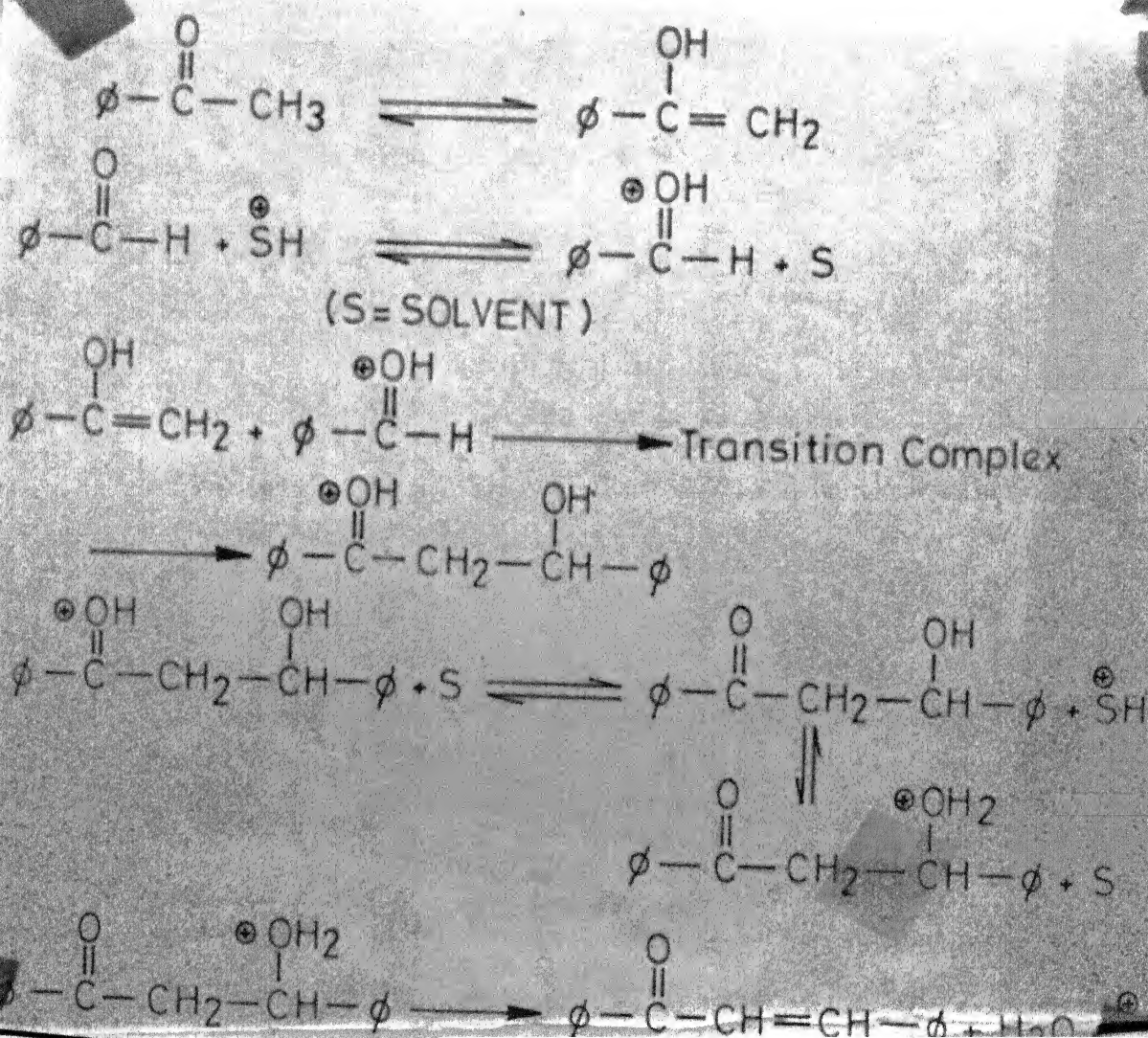
The substituted benzylideneacetophenones have likewise been obtained by condensing the appropriately substituted acetophenone with substituted benzaldehyde in the presence of alkali.

### Mechanism of chalcone formation

Kinetic studies have been reported for the base catalysed formation of chalcone<sup>3-5</sup> and its derivative<sup>5,6</sup>. Two alternative mechanisms (vide infra) have been advanced<sup>5</sup> for the reaction of

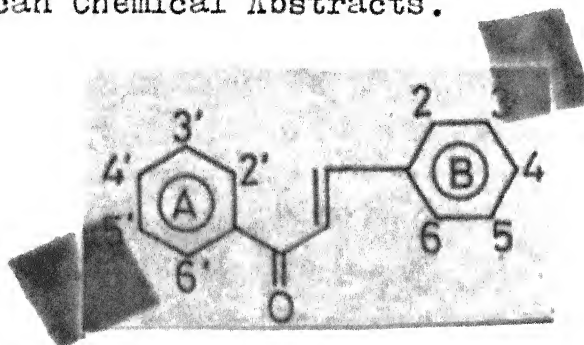


The formation of chalcone by the acid catalysed condensation of acetophenone and benzaldehyde has been studied<sup>7,8</sup>. The rate of reaction is reported<sup>7,8</sup> to depend upon the first power of the concentration of acetophenone, and first power of the concentration of benzaldehyde and upon the Hammett acidity function. Also, the condensation step (vide infra) has been shown to be the rate determining step in this reaction. The following mechanism seems to be operable:





NOMENCLATURE : Benzylideneacetophenone is the parent member of the chalcone series. The substituents in the benzene rings of chalcone are numbered as shown, and follow the pattern adopted by the American Chemical Abstracts.



The alternative names<sup>9</sup> given to chalcone are: phenyl styryl ketone, benzalacetophenone,  $\beta$ -phenylacrylophenone,  $\gamma$ -oxo- $\alpha$ , $\gamma$ -diphenyl- $\alpha$ -propylene, and  $\alpha$ -phenyl- $\beta$ -benzoyl-ethylene.

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CHAPTER - 2

## SYNTHETIC METHODS

By Claisen-Schmidt Reaction.....	7
From Chalcone $\alpha$ , $\beta$ -dibromides.....	9
From Schiff's Bases.....	10
From Organometallic Compounds.....	10
By Wittig Reaction.....	12
From Enamine and Aromatic Aldehydes.....	12
By Oxidative Decarboxylation of Oxo-acids.....	13
By Photo-Fries Reaction.....	13
From Benzal Chloride and Acetophenone.....	13
From Methyl Benzylphenacyl Sulphonium Hydroxide....	14
From $\alpha$ -Diazoacetophenone.....	14
From $\alpha$ -Epoxychalcones.....	14
From Cinnamic Acid Anhydride.....	14
From Cinnamic Acid and Phenol.....	15
From Cinnamoyl Chloride and Benzene.....	15
From Cinnamoyl Chloride and Phenol.....	15
From $\beta$ -Benzoylacrylic Acid.....	16
From $\beta$ -Chlorovinyl Ketone.....	16
From Flavanones.....	17
From 2-Diethylamino-1,3-Diphenyl-2-propen-1-one....	17

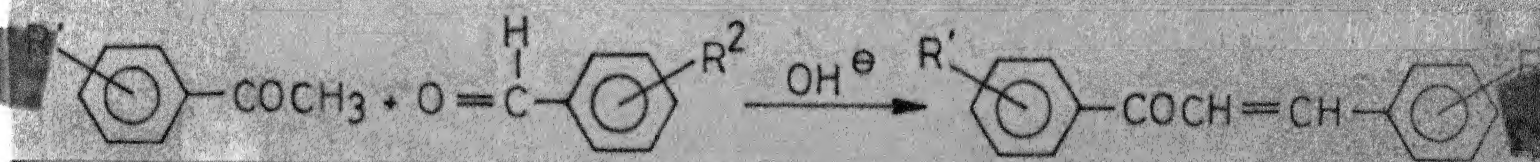


### MISCELLANEOUS EXAMPLES

Analogues of Carthamin.....	18
Sophoradin.....	18
$\alpha$ -Aminochalcones.....	20
$\alpha$ -Hydroxychalcones.....	20
Quinochalcones.....	21
Chromenochalcones.....	21
$\alpha$ -Arylazo- $\beta$ -arylchalcones.....	22
$\alpha$ -2'-Diacetoxy-3,4,4',6'-tetramethoxychalcone.....	23
References.....	23

### By Claisen-Schmidt Reaction:

A variety of methods are available for the synthesis of chalcones (vide infra). The most convenient method is the one which involves Claisen-Schmidt condensation of equimolar quantities of a substituted acetophenone with substituted benzaldehyde in the presence of aqueous alcoholic alkali.<sup>1-36</sup>



In the Claisen-Schmidt reaction, the concentration of alkali used usually range between 10-60%.<sup>7,8,21,23,26</sup> The reaction is carried out at about 50° for 12-15 hours, at room temperature for one week.<sup>7</sup> Under these conditions, however, Cannizzaro reaction<sup>37</sup> also takes place and thereby decreases the yield

of the desired product. In order to avoid the disproportionation of aldehyde in the above reaction, the use of benzylidene diacetate in place of aldehyde has been recommended.<sup>38</sup>

Other condensing agents have been employed and include alkali metal alkoxide,<sup>23,25,39</sup> magnesium tert. butoxide,<sup>40</sup> potassium carbon compound,<sup>41</sup> ( $KC_8$ ), hydrogen chloride,<sup>42,43</sup> anhydrous aluminium chloride,<sup>44</sup> boron trifluoride,<sup>45</sup> phosphorous oxychloride,<sup>46</sup> boric anhydride,<sup>47</sup> amino acids,<sup>48</sup> borax<sup>49</sup> and organocadmium compound,<sup>50</sup> e.g.,  $CdEt_2$  in butyl ether.

In the synthesis of polyhydroxy-chalcones by Claisen-Schmidt reaction, the higher concentration of alkali as a condensing agent is desirable. Chalcones having a 2'-hydroxy function, however, may cyclise to the corresponding flavanones under the above conditions.<sup>98</sup> This difficulty has, however, been overcome by protecting the 2'-hydroxyl group of substituted acetophenone (as methoxymethyl ether)<sup>121</sup> before their reaction with aromatic aldehydes. This procedure is claimed<sup>121</sup> to provide a route to the synthesis of otherwise inaccessible 2'-hydroxy chalcones.

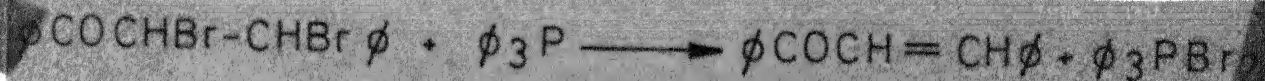
The use of acid catalyst, HCl in preference to alkali, has been recommended, for example, in the synthesis of cyanomethyl chalcones,<sup>42</sup> as well as hydroxynitrochalcones.<sup>43</sup> 2'-hydroxy-5-acetamido-chalcones have been synthesized involving the use of phosphorous oxychloride, which is claimed to be superior to alkali as a condensing agent.<sup>47</sup> Condensations have

been effected likewise in the presence of boric anhydride.<sup>47</sup> The water formed in this reaction is azeotropically distilled off with xylene. This method is reported to give good yield of chalcone.  $\alpha$ -(phenylthio)- and  $\alpha$ -(phenylsulphonyl) chalcones have been prepared<sup>51</sup> by the condensation of aromatic aldehydes with phenacyl phenyl sulphide and phenacyl sulphone respectively. The condensing agents employed in these reactions consisted of glacial acetic acid in combination with an organic base, viz., piperidine or benzylamine.

Chalcone in 50% yield has also been prepared by the reaction of acetophenone and benzaldehyde under the conditions of the Perkin reaction.<sup>122</sup>

From Chalcone  $\alpha, \beta$ -dibromides:

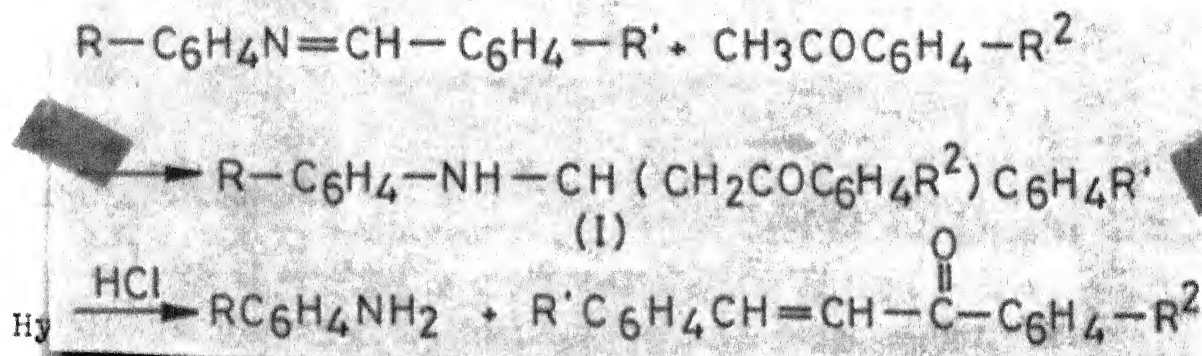
Debromination of chalcone  $\alpha, \beta$ -dibromide with one mole equivalent of trialkyl phosphine<sup>52,54</sup> yields chalcone in an excellent yield (92%). Triphenyl phosphine<sup>53</sup> likewise brings about debromination of the vicinal dibromo chalcone, thus:



Chaloone has also been secured by the debromination of chalcone  $\alpha, \beta$ -dibromide, either in the presence of chromous chloride<sup>55</sup> or by the action of potassium hydroxide in acetone medium.<sup>56</sup>

From Schiff's Bases:

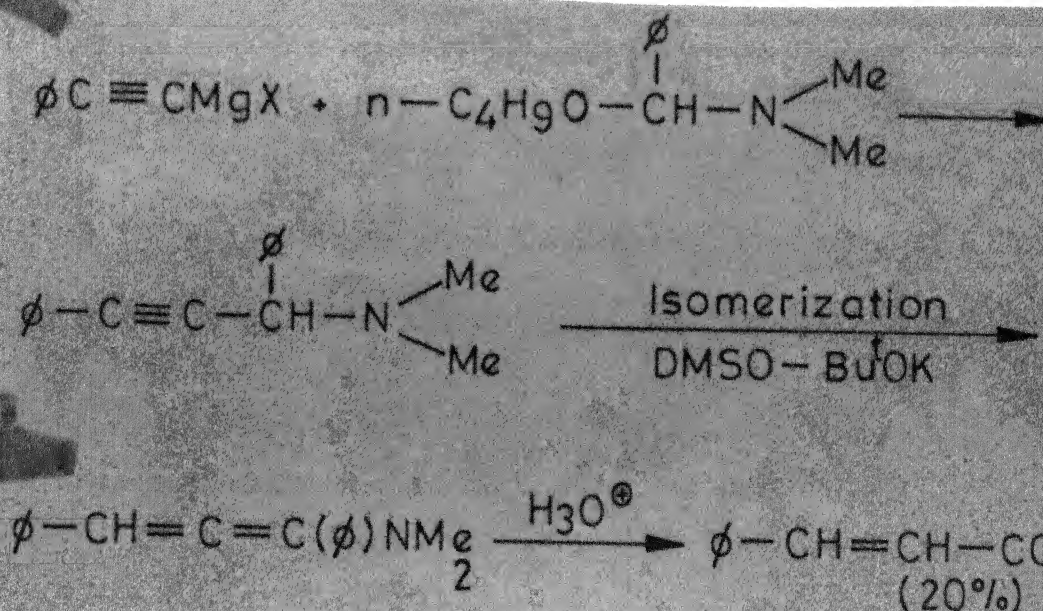
Schiff's bases are reported<sup>57-59</sup> to react with acetophenone and its derivative, in the presence of catalytic amount of amine hydrochloride, to yield  $\beta$ -arylamino ketone (I). On heating with concentrated hydrochloric acid, these ketones undergo the hydramine cleavage to yield primary aromatic amine and chalcone.



withdrawing substituents in  $\beta$ -arylamino ketones.

From Organometallic Compounds:

(a) Chalcone in 20% yield has been secured from acetylenic Grignard reagent<sup>61,123</sup> by carrying it through the following series of transformations:



The interaction of phenyl magnesium bromide and cinnam-nitrile with ammonium chloride is reported<sup>62</sup> to give an adduct, phenyl styryl ketimine dimer hydrochloride. The latter on hydrolysis, with dilute hydrochloric acid, furnished the chalcone.

Methyl magnesium iodide and benzaldehyde are reported<sup>63</sup> to react (in the absence of ether) to give chalcone, besides methyl phenyl carbinol. The formation of chalcone in this reaction arises due to the condensation of benzaldehyde with acetophenone formed by the oxidation of carbinol.

(b) Chalcone has been secured<sup>64</sup> (65%) by the interaction of appropriate cadmium derivative and cinnamoyl chloride in refluxing ether.

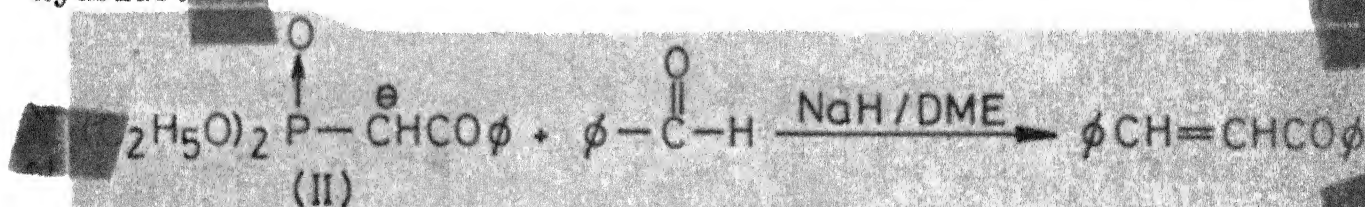
(c) The synthesis of chalcone (20-30%) has been achieved<sup>65</sup> by the action of styryl cyanide with phenyl lithium. Alternatively, chalcone (33%) can be prepared by reacting trans cinnamic acid<sup>65</sup> with phenyl lithium. Cis-cinnamic acid is reported<sup>65</sup> to react more rapidly than the trans isomer, yielding chalcone in a better yield (57%).

(d) Phenylacetylene<sup>66-68</sup> reacts with benzaldehyde, at room temperature, in the presence of  $\text{BF}_3$  in ether, to give chalcone in 60% yield. The Lewis acid,  $\text{BF}_3$ , enhances the positive nature of the carbonyl carbon, thereby facilitates the reaction.



### By Wittig Reaction:

Phosphorane of the general formula  $\text{Me}_n\text{Ph}_{(3-n)}\text{P}=\text{CHCOPh}$  ( $n = 0, 1, 2, 3$ ) are reported<sup>69-71</sup> to react with benzaldehyde to yield chalcone in good yields (70-90%). A patent<sup>72</sup> has appeared, which utilizes the Wittig reaction for the preparation of chalcone in 84% yield. Chalcone (60%) has also been obtained by the reaction of benzaldehyde with benzoylmethylene (p-dimethylaminophenyl) dimethyl phosphorane<sup>73</sup> or phosphonate carbanion,<sup>74</sup> II, derived from diethyl phenacyl phosphonate with sodium hydride:



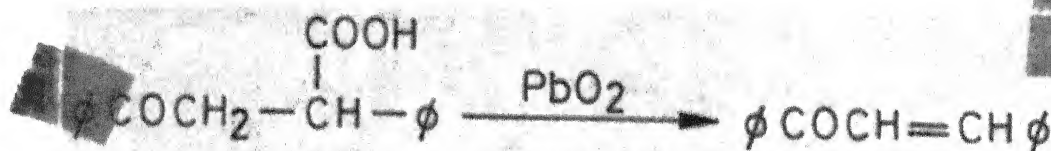
Alternatively,<sup>75</sup> the potassium derivative of diethyl phenyl phosphonate is reacted with an aromatic aldehyde (in dry toluene) to yield the desired chalcone. Several substituted chalcones have been prepared<sup>76</sup> by the reaction of carbonyl stabilized phosphonium and arsonium ylides with o-hydroxybenzaldehydes.

### From Enamines and Aromatic Aldehydes:

The synthesis of chalcone has also been effected by the interaction of benzaldehyde with N- $\alpha$ -styryl morpholine.<sup>77</sup>

From Oxidative Decarboxylation of  $\gamma$ -oxo Acids:

Lead dioxide is reported<sup>78</sup> to bring about the oxidative decarboxylation of 3-benzoyl-2-phenylpropionic acid to yield chalcone.



By Photo-Fries Reaction<sup>79-82</sup>:

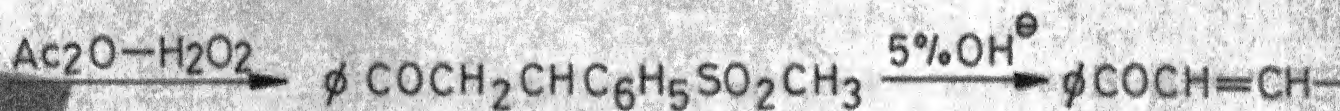
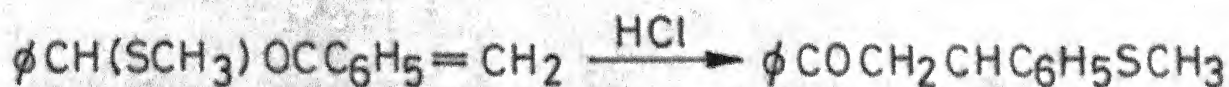
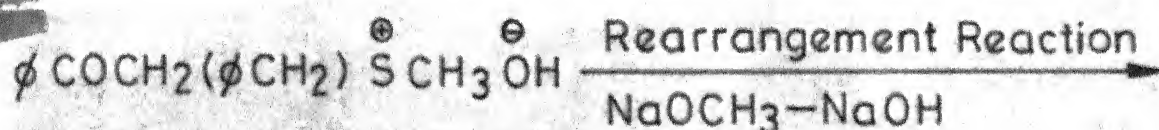
Photo-Fries rearrangement of phenyl cinnamates<sup>79,81,83</sup> has been exploited for the synthesis of 2'-hydroxychalcone (20-50%). The same reaction has been extended to the synthesis of 2',3'-; 2',4'- and 2',5'-dihydroxychalcones from the corresponding hydroxyphenyl cinnamates.<sup>80</sup> The synthesis of 2',3',5'-trihydroxychalcone has been achieved,<sup>84</sup> however, by the photolysis of 2,4-dihydroxycinnamate (the hydroxyl groups protected by methoxymethylation) followed by treatment with methanolic hydrochloric acid.

From Benzal Chloride and Acetophenone:

Chalcone, in 75% yield is reported<sup>85</sup> to be formed by heating at 120-130°, a mixture of benzal chloride and acetophenone in the presence of copper powder.

From Methyl Benzyphenacyl Sulphonium Hydroxide:

The synthesis of chalcone from methyl benzyphenacyl-sulphonium hydroxide<sup>86</sup> involves a number of synthetic steps, thus:



From  $\alpha$ -Diazoacetophenone:

Chalcone (8%) is reported to be formed when  $\alpha$ -diazoacetophenone is subjected to thermal decomposition.<sup>87</sup>

From  $\alpha$ -Epoxy Chalcones:

Chromous chloride in acetone medium brings about the reduction<sup>88</sup> of  $\alpha$ -epoxychalcone to give the corresponding chalcone in a low yield.

From Cinnamic Acid Anhydride:

Cadmium diphenyl<sup>89</sup> reacts with cinnamic acid anhydride to yield chalcone in 44% yield.



From Cinnamic Acid and Phenol:

Polyhydroxychalcones are obtained when cinnamic acid is condensed with phenols in presence of  $\text{BF}_3$ <sup>90-94</sup> or polyphosphoric acid.<sup>95</sup>

$\alpha$ -Alkylchalcones have been prepared,<sup>96</sup> though in poor yield, by the reaction, for example, of 1,3,5-trihydroxyphenol with  $\alpha$ -alkyl cinnamic acid, in the presence of acetic anhydride and polyphosphoric acid.

From Cinnamoyl Chloride and Benzene:

Chalcone (21%) along with 3-phenyl hydrindone (34%) are obtained<sup>97</sup> by the interaction of cinnamoyl chloride with benzene, in the presence of anhydrous aluminium chloride. The yield of chalcone is reported to be quantitative if chlorobenzene is also added to the reaction mixture.

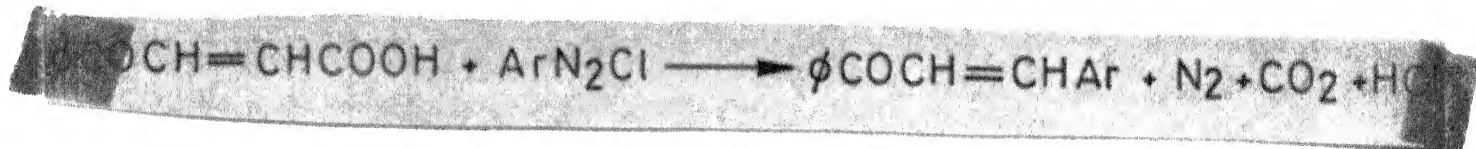
From Cinnamoyl Chloride and Phenol:

By using Behn's reaction polyhydroxychalcones have been synthesized.<sup>5</sup> It consists in the reaction of polyhydric phenols with cinnamoyl chloride, in nitrobenzene solvent, using aluminium chloride as the condensing agent. With phloroglucinol, however the initially formed 2',4',6'-trihydroxychalcone cyclises to give 5,7-dihydroxyflavanone as the major product. It is believed<sup>5</sup> that 6'-hydroxyl activates the 2'-hydroxyl to bring about the cyclisation.

Cinnamoyl chloride has likewise been condensed with phenolic ethers<sup>60,98,99</sup> in carbon disulphide to give the corresponding chalcones. The Friedel-Crafts reaction of cis-cinnamoyl chloride with n-butyl ether of thiophenol is reported<sup>100</sup> to give 4'-(n-butyl thio) chalcone.

From  $\beta$ -Benzoylacrylic Acids:

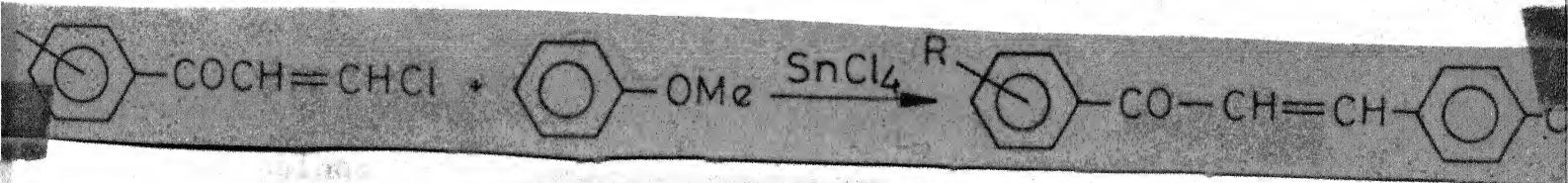
Aryl diazonium chlorides (carrying an electron withdrawing substituent) react with trans- $\beta$ -benzoylacrylic acid<sup>101,102</sup> to give chalcones.



The aryl group attacks the carbon atom  $\alpha$ - to the carboxylic group and this initial coupling is followed by decarboxylation.<sup>101</sup>

From  $\beta$ -Chlorovinyl Ketones:

Substituted  $\beta$ -chlorovinyl ketones have been condensed with phenolic ethers<sup>103-105</sup> in presence of stannic chloride to give chalcones in fairly good yield (47-65%).



A variation of the above reaction consists in the interaction of  $\beta$ -chlorovinyl ketone with aromatic hydrocarbons<sup>103</sup> and alkyl halides,<sup>103</sup> under the influence of  $\text{SnCl}_4$ , to give the corresponding chalcones.

From Flavanones:

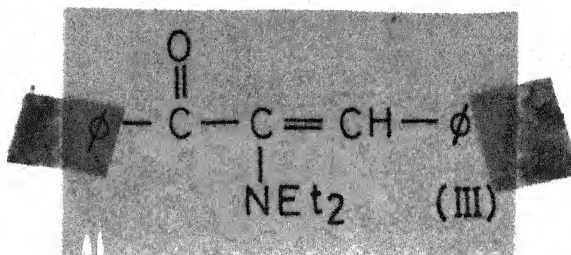
(a) Treatment of flavanones with alkali results in the opening of  $\gamma$ -pyrone ring and formation of 2'-hydroxy-chalcone.<sup>7,82,106-108</sup> Thus satisfactory yield of 2'-hydroxy-4,4',6'-trimethoxychalcone<sup>7</sup> has been obtained from 4',5,7-trimethoxyflavanone in the above manner.

(b) The micro-organism, Gibberella fukikuroi is capable of cleaving the oxygen heterocycle of flavanone to yield 2'-hydroxychalcone.<sup>109</sup> Part of the substrate undergoes ring opening, followed by microbial oxidation to yield the 2',4-dihydroxychalcone.

(c) UV irradiation of flavanone is reported<sup>110</sup> to yield three products, viz., 2'-hydroxychalcone (20%), 4-phenyl-dihydrocoumarin (13%) and salicylic acid (4%).

From 2-Diethylamino-1,3-Diphenyl-2-propen-1-one (III):

Chalcone (cis and trans) in 30% yield has been secured<sup>111</sup> by prolonged irradiation of the title compound in an ethereal solution:

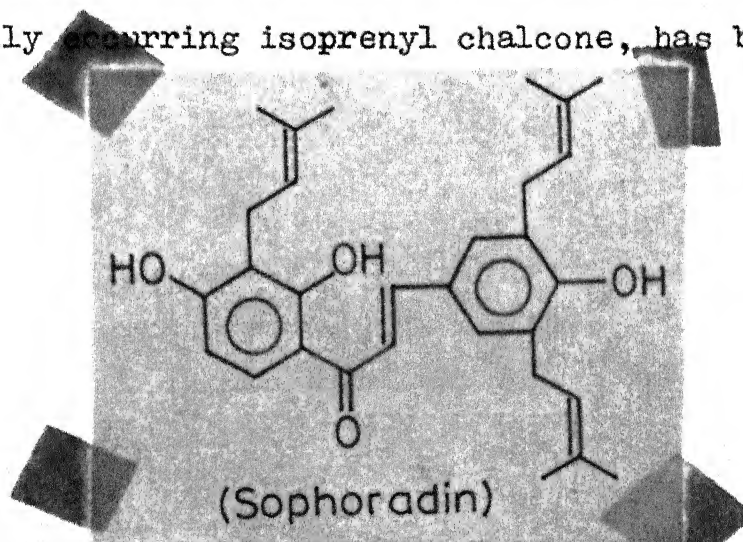


MISCELLANEOUS EXAMPLES:Analogues of Carthamin:

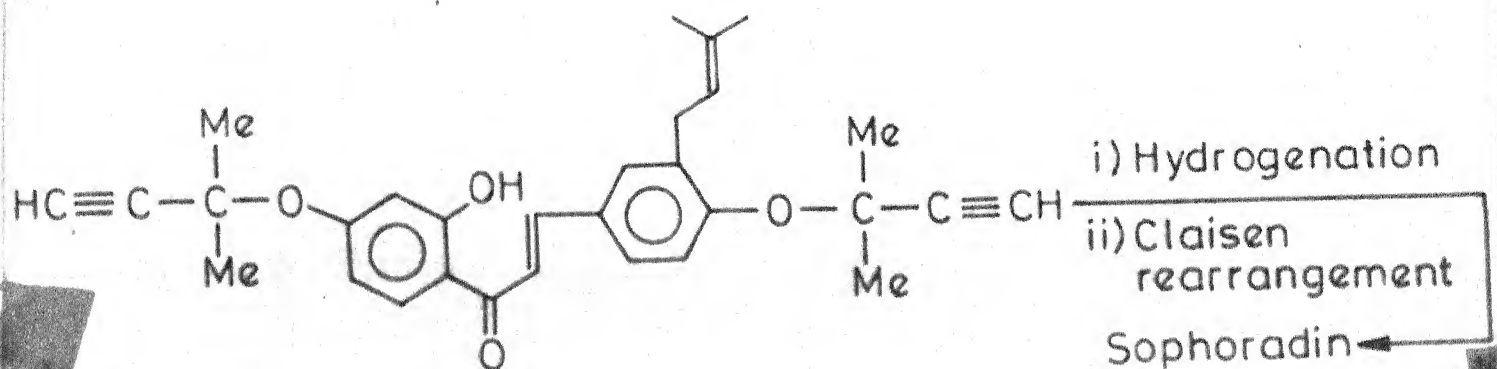
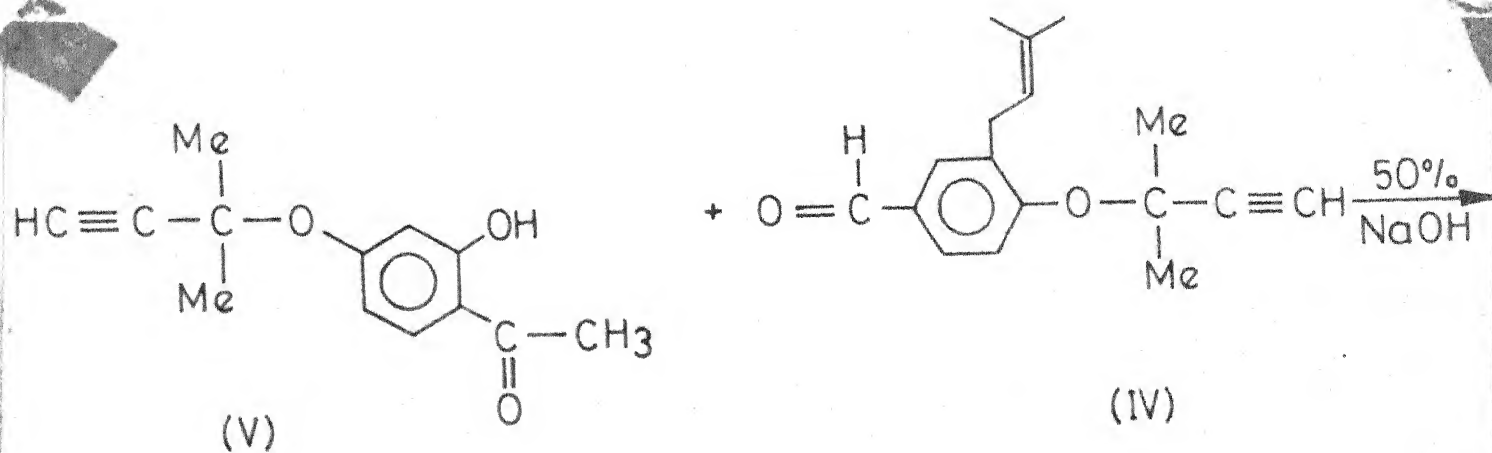
The syntheses of two analogues of carthamin, viz., 3'-methoxy-2',4,4',6'-tetrahydroxychalcone and 2'-methoxy-3',4,4',6'-tetrahydroxychalcone are reported<sup>112</sup> in the literature (cf. Method I). The hydroxylic functions in the reactants are protected by derivative preparation, viz., methoxymethylation, and are regenerated by hydrolysis toward the end of reaction.

Sophoradin:

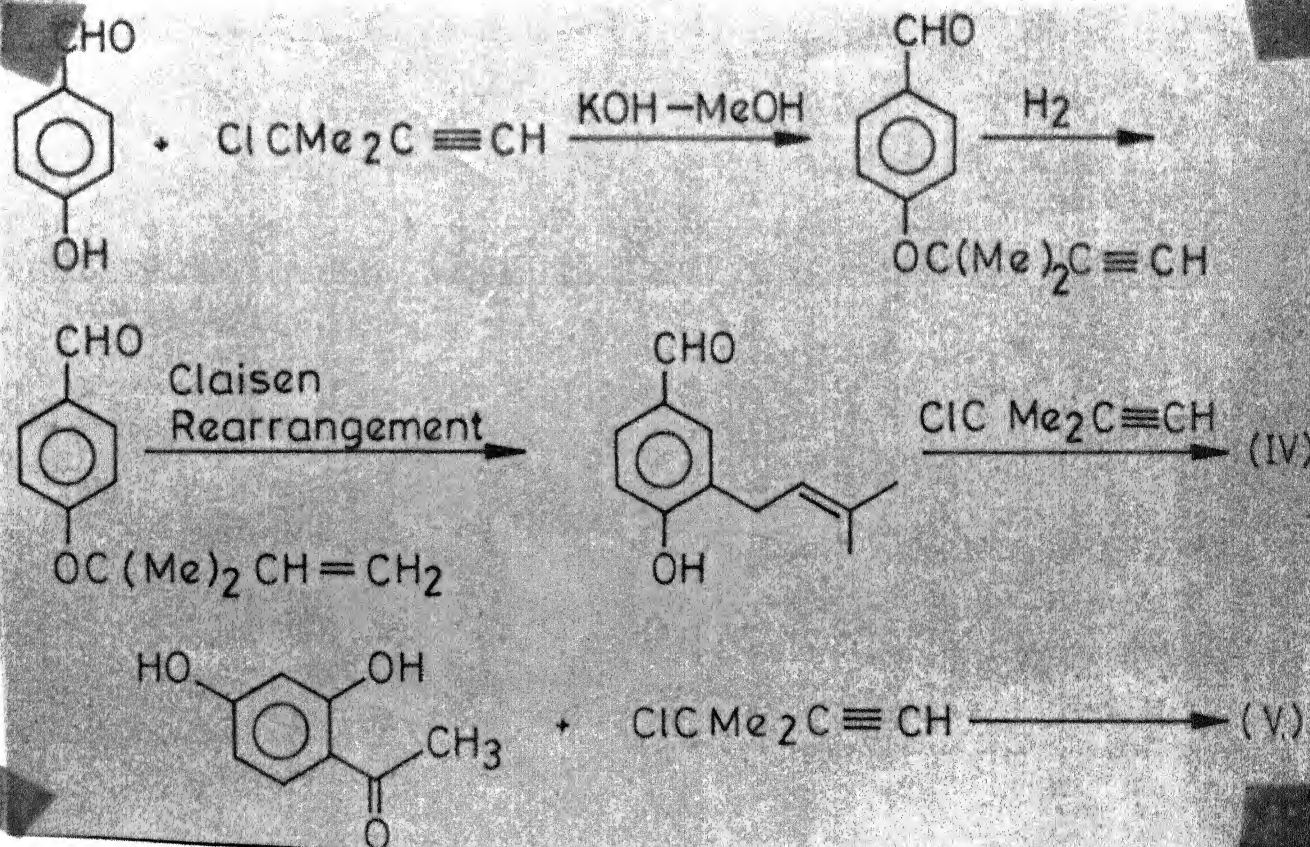
Based on the above reaction the synthesis of sophoradin, a naturally occurring isoprenyl chalcone, has been achieved.<sup>113</sup>



An alternate way of sophoradin synthesis is outlined:



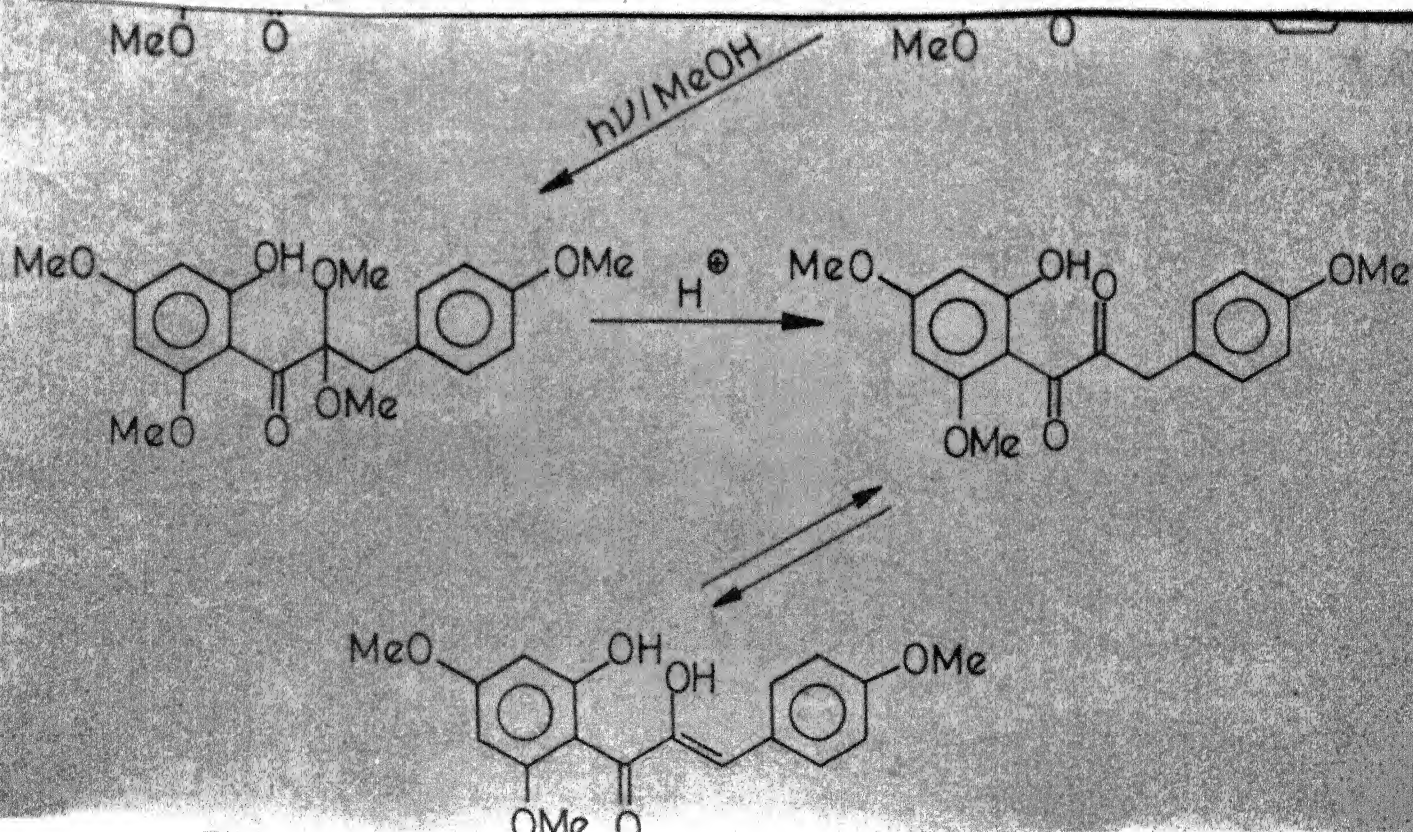
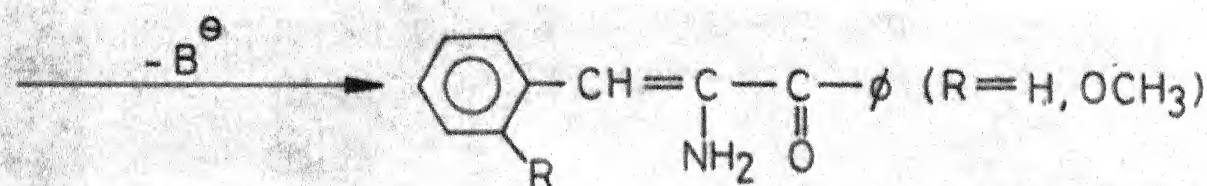
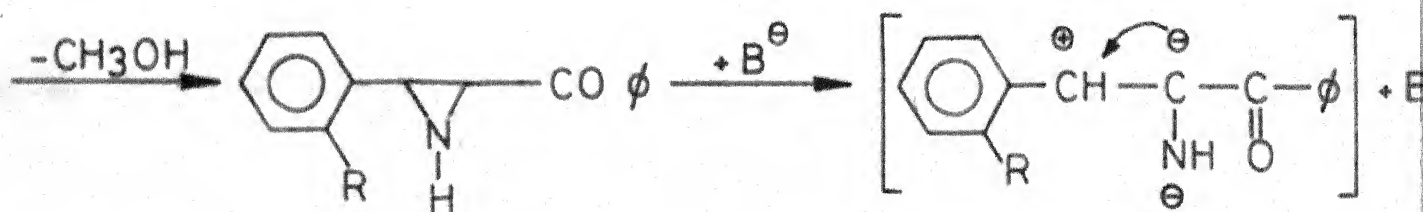
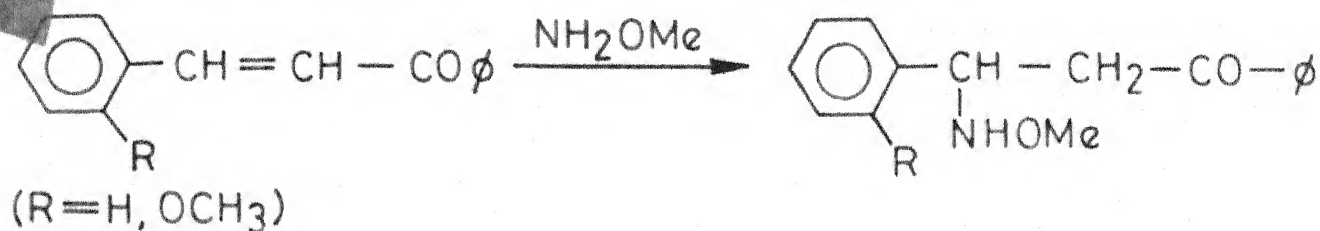
The starting materials (IV) and (V) are prepared as follows:





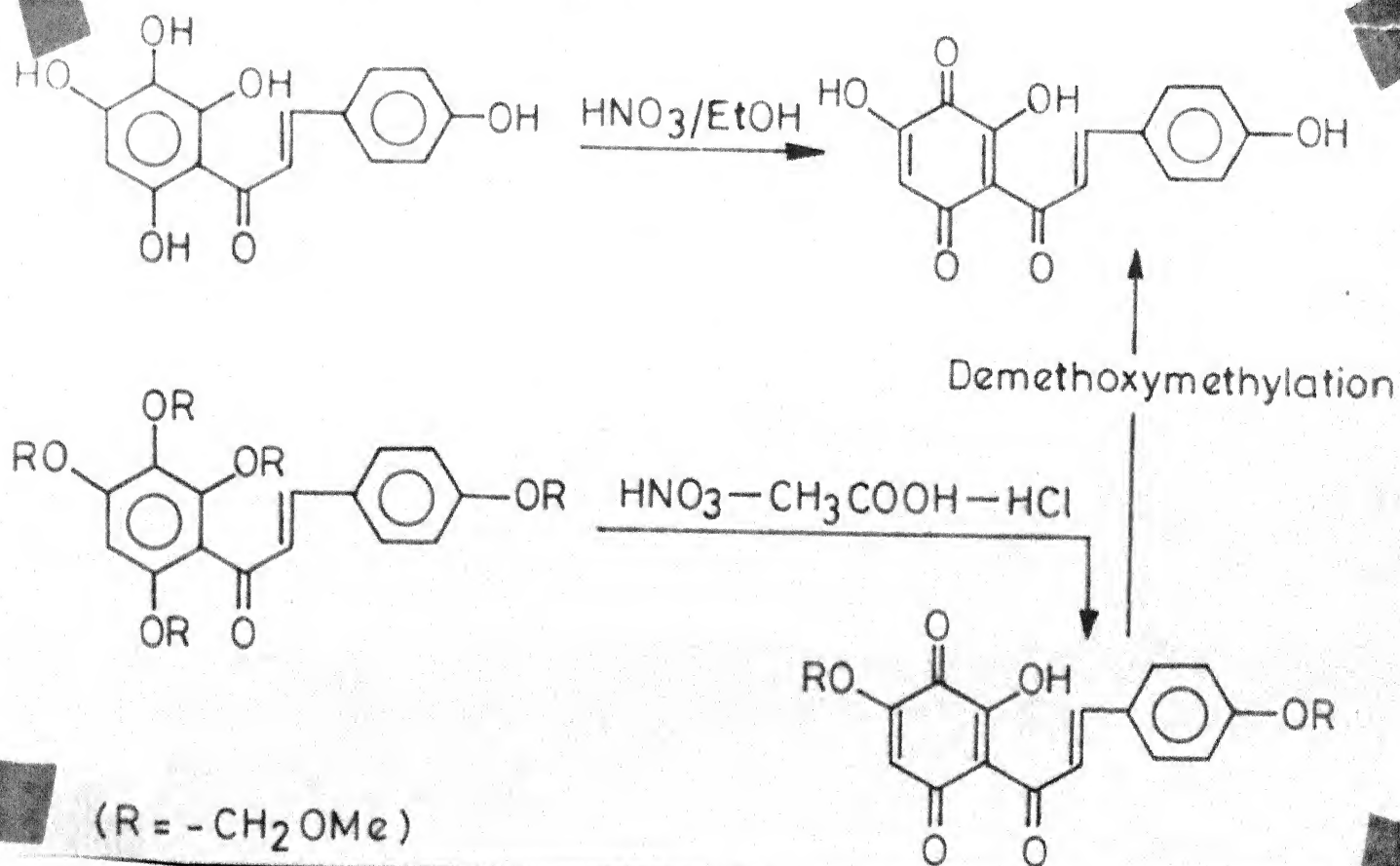
$\alpha$ -Aminochalcones:

The synthesis of  $\alpha$ -amino chalcones have been achieved<sup>115</sup> by the following series of reactions:



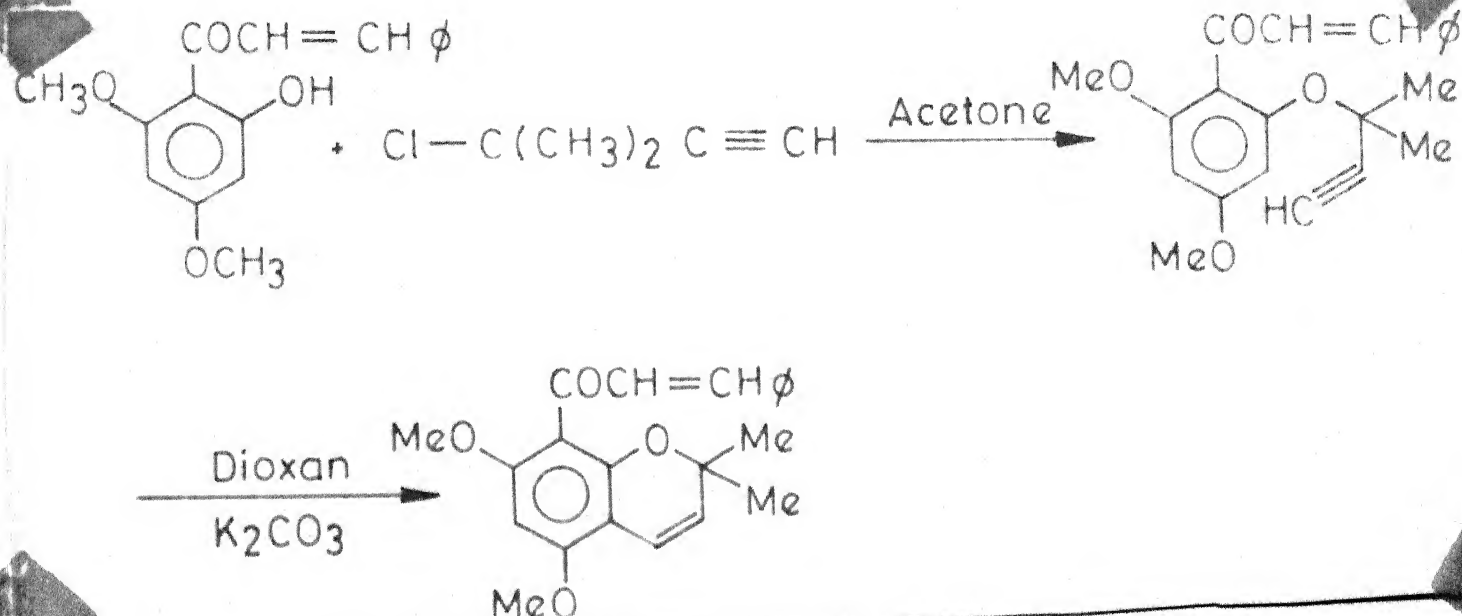
### Quinochalcones:

The synthesis of some quinochalcones has been achieved<sup>117</sup> by the oxidation of appropriately substituted hydroxychalcones. The preparation of 2',4,4'-trihydroxy-3',6'-quinochalcone serves as an illustrative example:



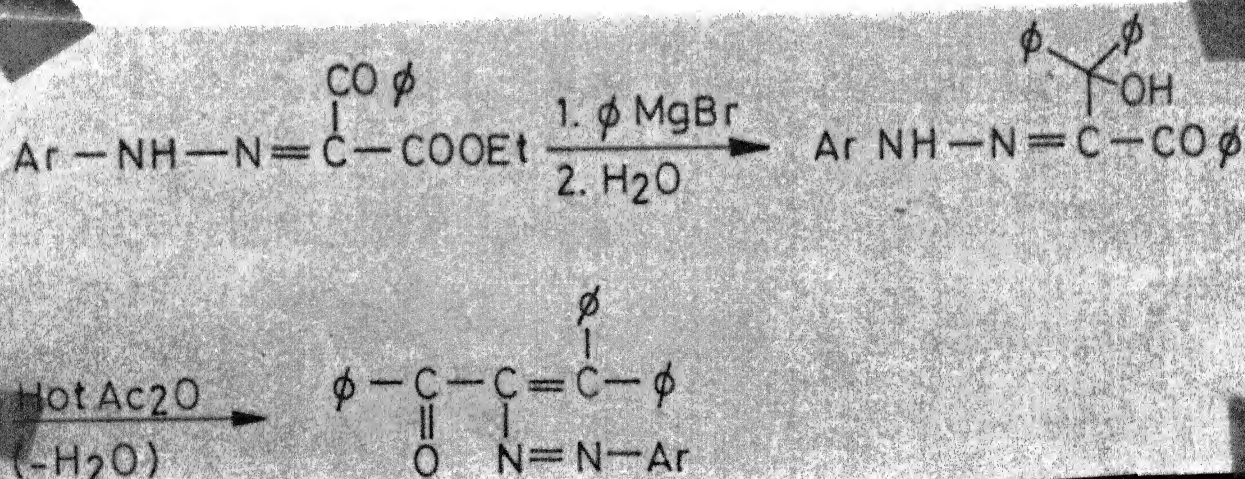
### Chromenochalcones:

A method for the preparation of chromenochalcone is described,<sup>118</sup> and involves the following steps:



### $\alpha$ -Arylazo- $\beta$ -arylchalcones:

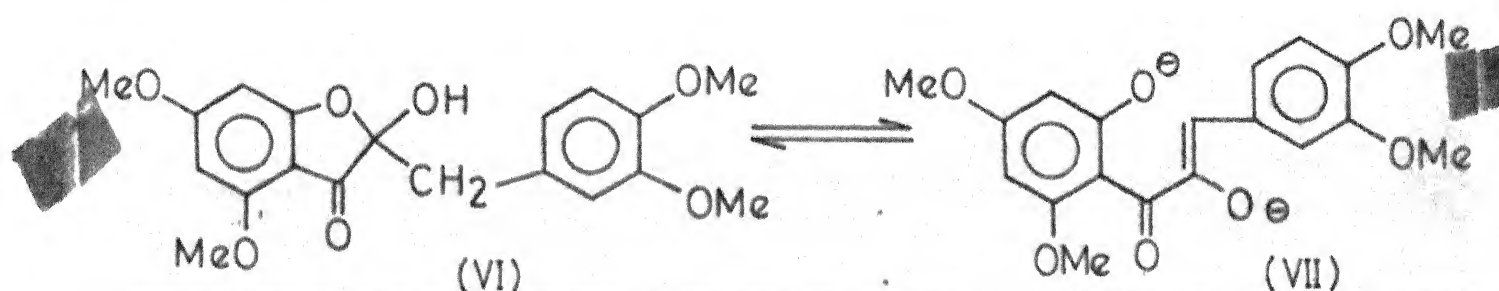
Starting from  $\alpha, \beta$ -diketoesters;  $\alpha$ -arylazo- $\beta$ -arylchalcones have been synthesized.<sup>119</sup> Thus,





$\alpha$ ,2'-Diacetoxy-3,4,4',6'-tetramethoxychalcone:

The synthesis of  $\alpha$ ,2'-diacetoxy-3,4,4',6'-tetramethoxychalcone from 2-benzyl-2-hydroxycoumaran-3-one (VI) is described.<sup>120</sup> Advantage is taken of the fact that the coumaranone in alkaline medium exists in equilibrium with the corresponding chalcone anion (VII).



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CHAPTER - 3

## SOME CLASSES OF CHALCONES AND CHALCONE ANALOGUES

## Substituted Chalcones

Hydroxynitrochalcones.....	33
Hydroxychalcones.....	34
Methoxychalcones.....	35
Carboxychalcones and Chalcone Analogues.....	36
Isop <sup>ren</sup> <del>ent</del> ylchalcones.....	36
Phosphorlyated and Sulphuric Acid Esters of Chalcones..	36
Phenylchalcones.....	36
Polyfluorochalcones.....	37
Heterocyclic Chalcone Analogues.....	37
References.....	39

SUBSTITUTED CHALCONESHydroxynitrochalcones:

Several hydroxynitrochalcones<sup>1-11</sup> have been prepared involving the Claisen-Schmidt condensation. This condensation has been effected with a variety of condensing agents, viz., aqueous alkali,<sup>12-17</sup> sodium methylate, piperidine,<sup>14</sup> aluminium chloride,<sup>12,14,18</sup> boron trifluoride,<sup>14</sup> and dry hydrogen chloride.<sup>14-16</sup> The preparation of  $\alpha$ -methylchalcones (containing a nitro group) by the interaction of hydroxynitropropiophenone

with various aldehydes is also reported in the literature.<sup>19</sup> It has been suggested<sup>20</sup> that dypones may be the possible intermediates in the synthesis of nitrohydroxychalcones.

In general the electron donating substituents<sup>16</sup> (low Hammett Constant) in the aldehydic component, and the electron withdrawing substituents (high Hammett constant) in the ketone,<sup>21</sup> favour the Claisen-Schmidt condensation by HCl. On the other hand the electron withdrawing substituent<sup>15</sup> in the aldehydic component, favour condensation by caustic alkali.

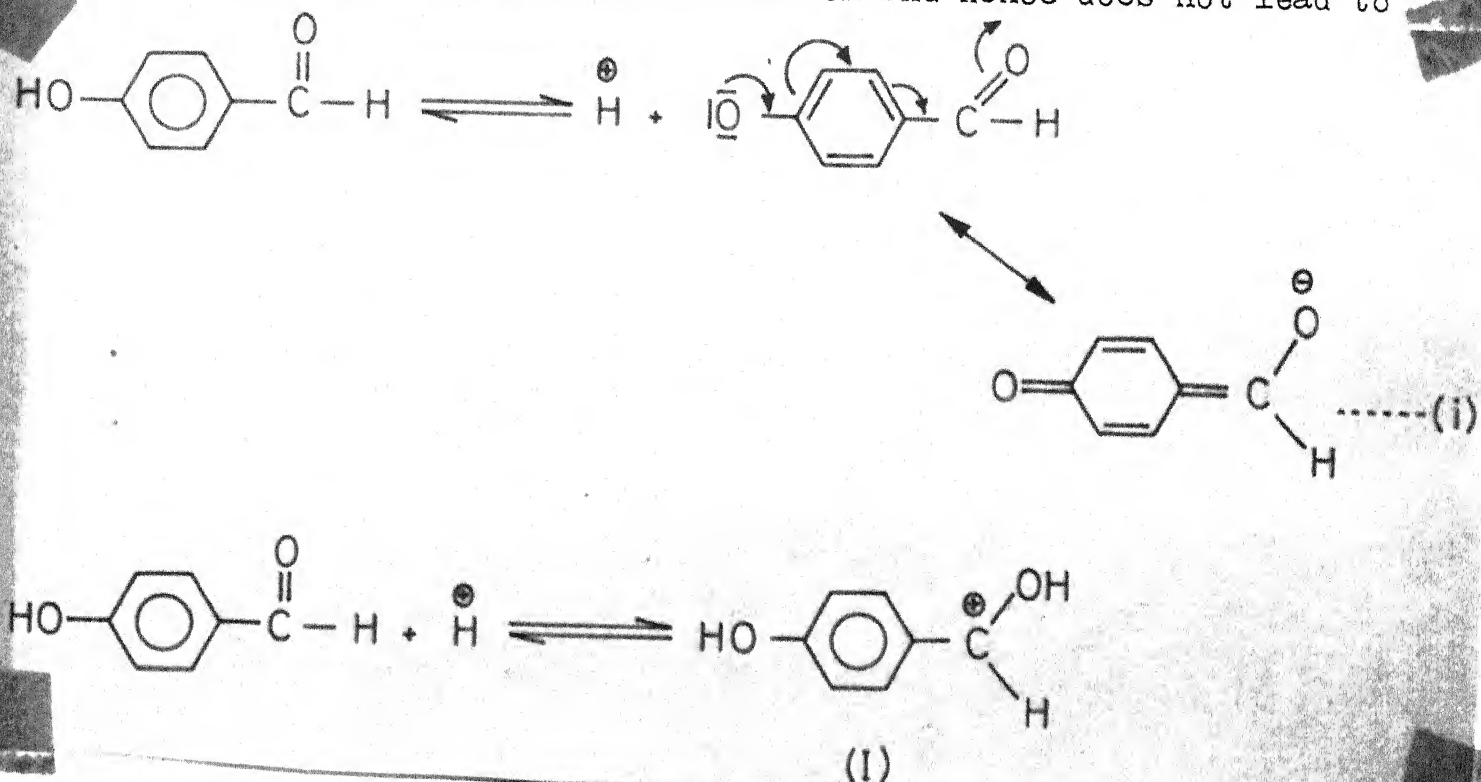
The preparation of a large number of substituted chalcones, which include hydroxy-, methoxy- and carboxychalcones are reported<sup>22-48</sup> in the literature.

#### Hydroxychalcones:

Some of the difficultly preparable 2'-hydroxychalcones have been synthesized in excellent yields, by converting the 2-hydroxy group of 2-hydroxyacetophenone to corresponding methoxymethyl ether,<sup>49</sup> prior to Claisen-Schmidt condensation. The hydroxychalcone is then regenerated by treatment with hot acid.

The synthesis of chalcones derived from 2-hydroxy acetophenone,<sup>50</sup> 2'-hydroxy-4-ethoxyacetophenone,<sup>51</sup> 2-hydroxy-4-n-butoxyacetophenone<sup>52</sup> and 2-hydroxy-4-n-propoxy-5-bromo (or nitro)-acetophenone<sup>53-55</sup> have also been reported. The preparation of polyhydroxychalcones derived from resacetophenone<sup>32,56</sup> and quinacetophenone<sup>57</sup> has been secured likewise.

The reaction of *p*-hydroxybenzaldehyde with substituted acetophenone is claimed<sup>58</sup> to proceed well in acid than in alkaline medium. This observation has been rationalised<sup>58</sup> as follows: In alkaline medium, reaction (i) is favoured, which obviously lowers the reactivity of the carbonyl carbon and hence does not lead to



In acid medium, however, the dissociation of the phenol is restricted and the formation of carbonium ion (I) is facilitated. These effects, therefore, exert a favourable influence of chalcone formation.

#### Methoxychalcones:

The syntheses of a large number of methoxychalcones,<sup>59,60</sup> including those derived, from quinacetophenone monomethyl ether<sup>61</sup> and resacetophenone dimethyl ether,<sup>56</sup> are described in literature.



### Carboxychalcones and Chalcone Analogues:

Carboxychalcones,<sup>62,63</sup> including the chalcone derived from caffeic acid<sup>64</sup> have been prepared by the usual Claisen-Schmidt reaction. In general the ketone required in the reaction are derived by the Fries migration of *o*- and *p*-acetoxybenzoic acids.

The naphthalene,<sup>65-72</sup> phenanthrene,<sup>66</sup> anthracene<sup>66</sup> and bicyclic<sup>73</sup> analogue of chalcones have also been prepared.

### Isop<sup>ren</sup>tylchalcones:

The synthesis of several naturally occurring isop<sup>ren</sup>tyl chalcones<sup>74,75</sup> have been accomplished by employing Claisen-Schmidt reaction, viz., cordoin,<sup>75</sup> isocordoin,<sup>75</sup> 4-hydroxycordoin,<sup>75</sup> derricin,<sup>75,77</sup> 4-hydroxyderricin,<sup>75</sup> sophoradin,<sup>76</sup> and derricidin.<sup>77</sup>

### Phosphorylated and Sulphuric Acid Esters of Chalcones:

The preparation of title compounds<sup>78,79</sup> have been achieved by Claisen-Schmidt reaction

### Phenylchalcones:

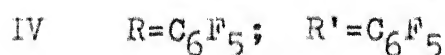
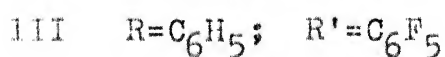
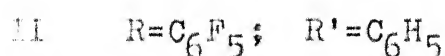
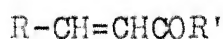
The synthesis of 4- (and 4'-) phenylchalcones<sup>80</sup> and  $\alpha$ - (and  $\beta$ -) phenylchalcones<sup>81-83</sup> are described in the literature.

The preparation of  $\alpha$ -phenylchalcone<sup>82</sup> has been secured by the interaction of appropriately substituted acrylyl chloride with phenol in the presence of aluminium chloride. On the other hand 4'-nitro- $\alpha$ -phenylchalcone has been obtained<sup>83</sup> by the

reaction of 4'-nitrodesoxybenzoin with ethyl benzylideneacetoacetate under the influence of ethanolic sodium methoxide.

#### Polyfluorochalcones:

The polyfluorochalcones (II-IV) have been synthesized<sup>84</sup> by the Claisen-Schmidt reaction:



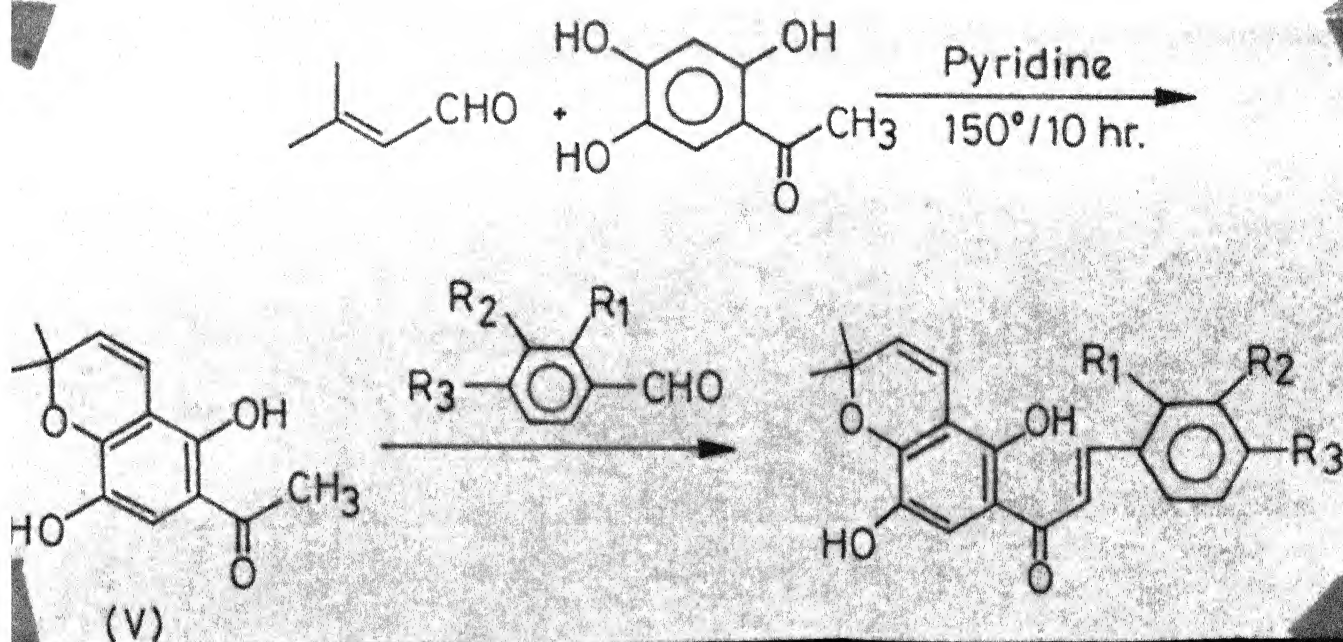
In the synthesis of IV, a lower concentration of alkali (1.5%) has been recommended.<sup>84</sup> With higher concentration of alkali, the initially formed polyfluorochalcone undergoes a haloform type of cleavage<sup>84</sup> leading to the formation of 2,3,4,5,6-pentafluoro-trans-cinnamic acid and pentafluorobenzene.

#### Heterocyclic Chalcone Analogues:

A number of heterocyclic analogues of chalcones have been reported. These include the chalcone analogues of pyrrole,<sup>85,87</sup> indole,<sup>88,89</sup> carbazole,<sup>90</sup> furan,<sup>67,85,86,91-95</sup> thiophene,<sup>66,85,92,96-103</sup> selenophene,<sup>104</sup> pyridine,<sup>66,92,93,98,105-107</sup> quinoline,<sup>66,93</sup> 8-hydroxyquinoline,<sup>108</sup> piperidine,<sup>109</sup> 1,4-benzodioxans,<sup>110</sup> pyridone,<sup>111</sup> pyrimidine,<sup>112</sup> pyrazole<sup>113</sup> and acridine.<sup>114</sup>

Several chalcone analogues have been prepared by the Claisen-Schmidt reaction, viz., ferrocene,<sup>115,116</sup> cymantrene,<sup>117</sup> benzo-chrotrene,<sup>117</sup> cinnamoyl<sup>118</sup> chromono,<sup>122</sup> ohromeno<sup>123,124</sup> and coumarinochalcones.<sup>119</sup>

The syntheses of chromenochalcone<sup>120</sup> including Flemi-Chapparin A have been achieved (53-63%) by the reaction of 6-acetyl-5,8-dihydroxy-2,2-dimethylchromene (V) and substituted benzaldehydes:



The preparation of some  $\alpha$ -aroylchalcones involving Knoevenagel reaction between diaroylmethanes and aromatic aldehydes has also been described.<sup>121</sup>

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## P A R T - II

CHAPTER - 4.1

## REACTION OF CHALCONES WITH REDUCING AGENTS

## Catalytic Hydrogenation

Reduction of Olefinic Group.....	51
Reduction of Carbonyl Group.....	52
Reduction of Olefinic and Carbonyl Groups.....	52
Saturation of Olefinic Bond and Reduction of Carbonyl to Methylene Groups.....	53
Reduction of Aromatic Rings and Enone Function.....	53

## Complex Metal Hydride Reduction

Alkali Metal Borohydrides.....	<del>55</del> 53
LAH and <del>Trimethoxy Aluminium Hydride</del> <sup>Lithium trimethoxyaluminum hydride</sup> .....	55
Lithium Aluminium Hydride-Aluminium Chloride.....	<del>57</del> 55
Organotin Hydrides.....	57
Electrolytic Reduction.....	<del>59</del> 57
Meerwein-Ponndorf-Verley Reduction.....	59
Reduction by Metals.....	<del>61</del> 59
Willgerodt-Kindler Reaction.....	61
Reduction by 'Hantzsch Ester'.....	61
Reduction by Pyridine-Borane Reagent.....	<del>62</del> 61
Reduction by Terpenes.....	62
Miscellaneous Reductions.....	62
References.....	62

Catalytic HydrogenationReduction of Olefinic Group<sup>1-11</sup>:

Chalcone on catalytic hydrogenation<sup>1-4,10</sup> with Raney nickel, in ethanol, yields benzylacetophenone. The latter compound has been secured<sup>5</sup> in high yield (96%) by employing dichloroethane in place of ethanol as a solvent. High pressure hydrogenation (50-120 atmospheres) of chalcone, in the presence of a non-pyrophoric Raney nickel catalyst (composition: copper, 58-60% and aluminium, 40-42%) is reported<sup>6</sup> to yield dihydrochalcone (75%).

Chalcones have been reduced by hydrogen and platinum to hydrochalcones,<sup>7</sup> which in turn can be reduced to hydrochalcals.

ortho-Hydroxychalcone<sup>8</sup> is reduced completely to the corresponding dihydrochalcone, in ether, in the presence of platinum black, by a current of hydrogen. The preparation of several dihydrochalcones is described in literature.<sup>55-66</sup>

With platinum oxide catalyst in ethanol (alkaline) the hydrogenation of chalcone stops with the absorption of one molecule of hydrogen and the exclusive formation of saturated ketone.<sup>9</sup> A study is reported<sup>10</sup> in respect of controlling catalytic hydrogenation (catalyst: platinum oxide) of chalcone under the influence of added ferric chloride, different solvents and temperature. Thus the saturation of the ethylenic bond occurs<sup>10</sup> very smoothly either in cold benzene, toluene or boiling acetic acid.

$\text{Pd}_3\text{B}_2$  is reported<sup>11</sup> to be an efficient catalyst in the selective hydrogenation of olefinic double bond in chalcone. It has, therefore, been employed<sup>11</sup> as a catalyst in the quantitative microhydrogenation of such types of compounds.

#### Reduction of Carbonyl Group:

*p*'-Methylchalcone is reduced by hydrogen to the corresponding unsaturated secondary alcohol,<sup>12</sup> using platinum black and large excess of ferric chloride.

Selective reduction of the carbonyl group in chalcone has likewise been achieved<sup>13</sup> by using optimum amount of palladium catalyst (promoters: ferrous sulphate-zinc acetate) at ordinary atmospheric pressure and room temperature. Hydrogenation of chalcone, at atmospheric pressure, with colloidal palladium or with palladium precipitated on animal charcoal, is reported<sup>14</sup> to reduce smoothly the carbonyl group.

#### Reduction of Olefinic and Carbonyl Groups:

1,3-Diphenylpropanol<sup>5</sup> has been secured by the catalytic hydrogenation of ethanolic solution of chalcone with Raney-nickel. According to a report,<sup>4</sup> the same transformation has been accomplished, in 45 minutes, by incorporating traces of alkali in the reaction medium.

### Saturation of Olefinic Bond and Reduction of Carbonyl to Methylene Group:

Catalytic reduction of chalcone by hydrogen in presence of nickel (reduced at 250°, and partially deactivated at 200°) yields 1,3-diphenylpropane. A quantitative yield of this compound is obtained by the catalytic hydrogenation of chalcone with platinum catalyst<sup>9</sup> in ethanol, in presence of concentrated hydrochloric acid.

### Reduction of Aromatic Rings and Enone Function:

Chalcone undergoes hydrogenation in presence of activated nickel catalyst, at elevated temperature to give dicyclohexylpropane.<sup>53, 49</sup> Formation of a similar perhydro compound is reported<sup>12</sup> in the case of p'-methylchalcone, involving the use of platinum black as a catalyst.

### Complex Metal Hydride Reduction

#### Alkali Metal Borohydrides:

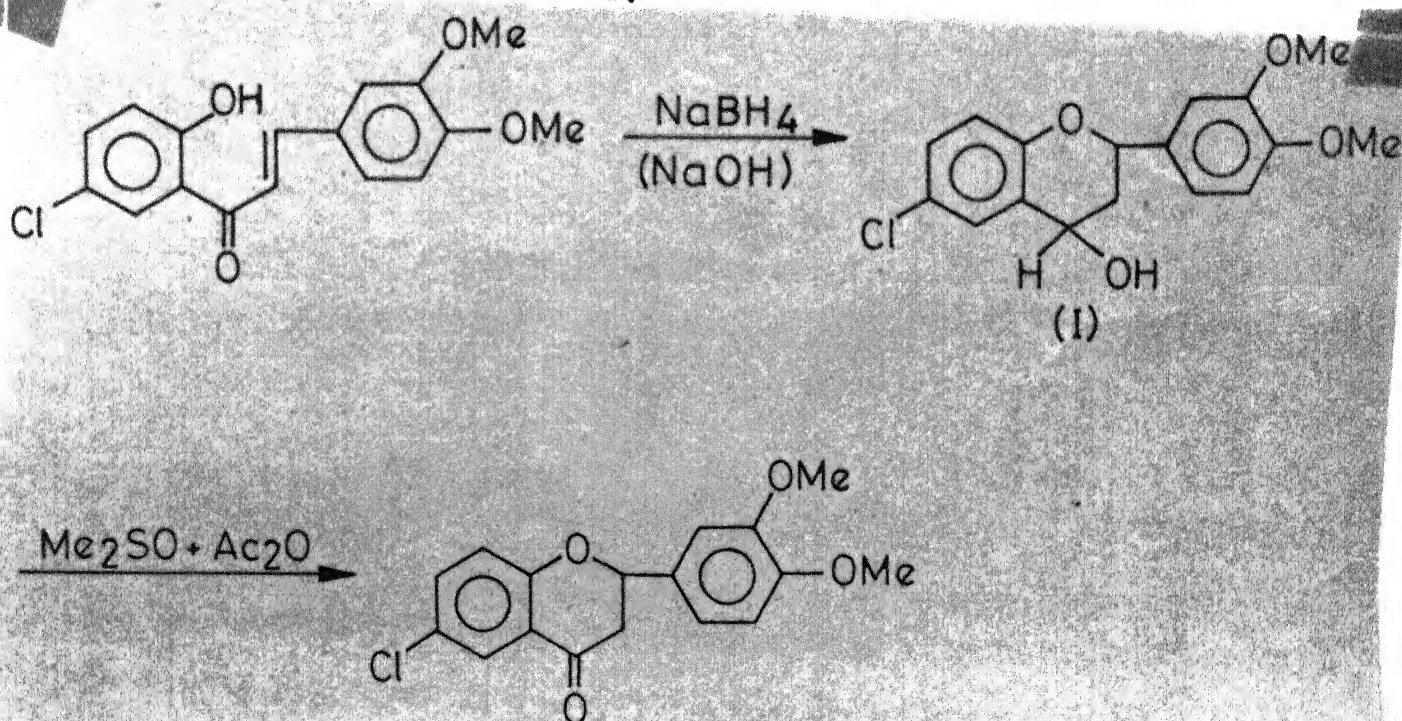
Selective reduction of the double bond in chalcone occurs, when it is reacted in pyridine, with sodium borohydride.<sup>15</sup>

Chalcone on treatment with potassium borohydride in water or methanol yields the corresponding carbinol.<sup>16-18</sup> This reaction has been extended for the preparation of several substituted allyl alcohols.<sup>19,20</sup> The selective reduction of



carbonyl group of chalcone has been achieved<sup>17</sup> by potassium borohydride and aluminium isopropoxide in isopropyl alcohol. The resulting compound often referred to as chalcol (1,3-diphenyl-2-en-1-ol) on treatment with alkali is reported<sup>17</sup> to undergo a rearrangement to yield the dihydrochalcone.

Sodium borohydride reduction of 2'-hydroxychalcone is reported<sup>21</sup> to yield flav-5-ene, besides the expected unsaturated alcohol. 1,3-Diphenyl-1 (and 2-) propanols<sup>22</sup> are obtainable in 85% yield by carrying out reduction of chalcone with sodium borohydride-boron trifluoride, followed by treatment with alkaline hydrogen peroxide. Using chalcone as the starting material the synthesis of flavanol (I) and its corresponding flavanone have been achieved.<sup>18</sup>



been suggested for this reduction.

Lithium Trimethoxyaluminum Hydride;  
LAH and Trimethoxyaluminium Hydride:

The reduction of chalcone with LAH can be controlled to yield either the unsaturated<sup>24</sup> or saturated alcohol.<sup>25</sup> This reaction has been exploited<sup>26</sup> in the synthesis of 4-cinnamylidene-2,5-cyclohexadien-1-ones. Thus 4'-hydroxychalcones have been reduced by LAH to the corresponding unsaturated alcohols, and the latter dehydrated to the aforesaid compounds. Chalcone is reported<sup>27</sup> to give the unsaturated alcohol as the major product, if LAH is replaced by the less aggressive reagent, *Lithium trimethoxyaluminum hydride*. viz., ~~trimethoxyaluminium hydride~~.

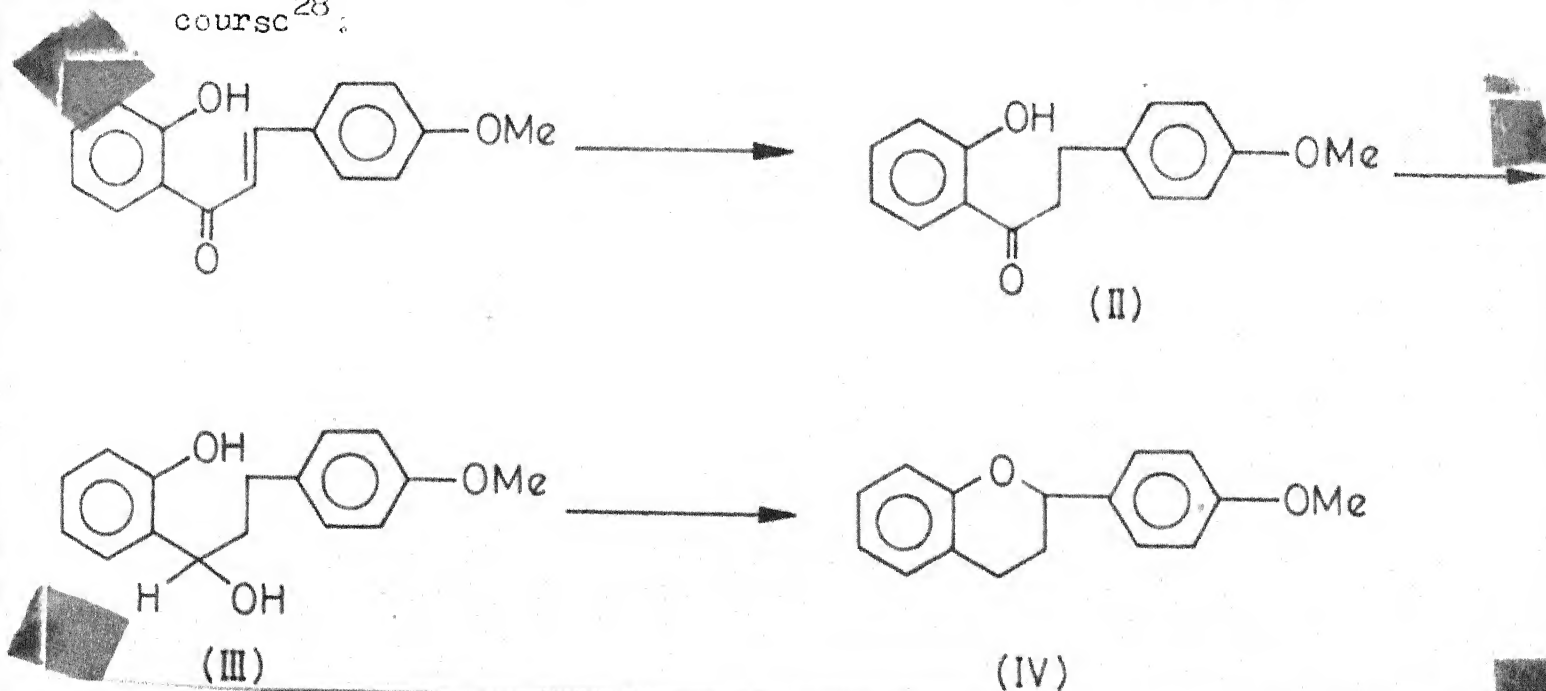
Lithium Aluminium Hydride-Aluminium Chloride (LAH-AlCl<sub>3</sub>):

Treatment of chalcone with LAH-AlCl<sub>3</sub> yields the corresponding propenes<sup>28</sup> and a dimer, 1,3,5-triphenyl-4-benzyl-1-pentene<sup>29</sup> (44-65%).

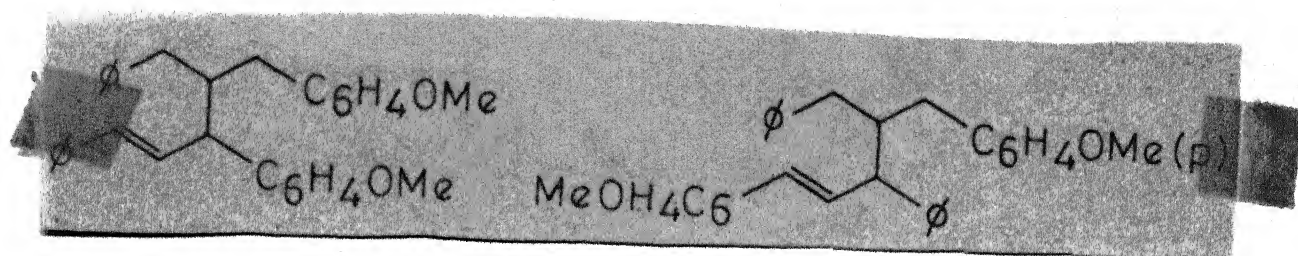
The mechanism of the reaction has been postulated<sup>28</sup> as follows: With lithium aluminium hydride, chalcone undergoes transformation to the saturated alcohol. The latter compound loses a molecule of water, under the influence of the added Lewis acid, aluminium chloride, to yield the 1,3-diphenyl-1-propene.

In the hydrogenolysis of some chalcones (vide infra) two isomeric disubstituted propenes have been obtained.<sup>28,30,31</sup> In one instance the formation of an additional compound, viz., 1-(*o*-hydroxyphenyl)-3-phenyl-1-propanone has been reported.<sup>30</sup>

It is interesting to note that 2-hydroxy-4'-methoxy-chalcones on hydrogenolysis yields three products;<sup>28</sup> viz., a saturated ketone (II), a secondary alcohol (III) and 4'-methoxy-flavan (IV). Apparently the reduction follows a different course<sup>28</sup>:



In the reduction of 4- and 4'-methoxychalcones by lithium aluminium hydride-aluminium chloride (1:2) two dimers are reported<sup>31</sup> to be formed, besides the isomeric 1,3-disubstituted propenes. The following structures have been postulated<sup>31</sup> for these dimers:



The behaviour of  $\alpha$ -(phenylsulphonyl) chalcone<sup>32</sup> towards mixed reagents (LAH- $\text{AlCl}_3$ ) is rather interesting. It results in the saturation of the ethylenic double bond giving the corresponding hydrochalcone.<sup>32</sup>

#### Organotin Hydride Reduction:

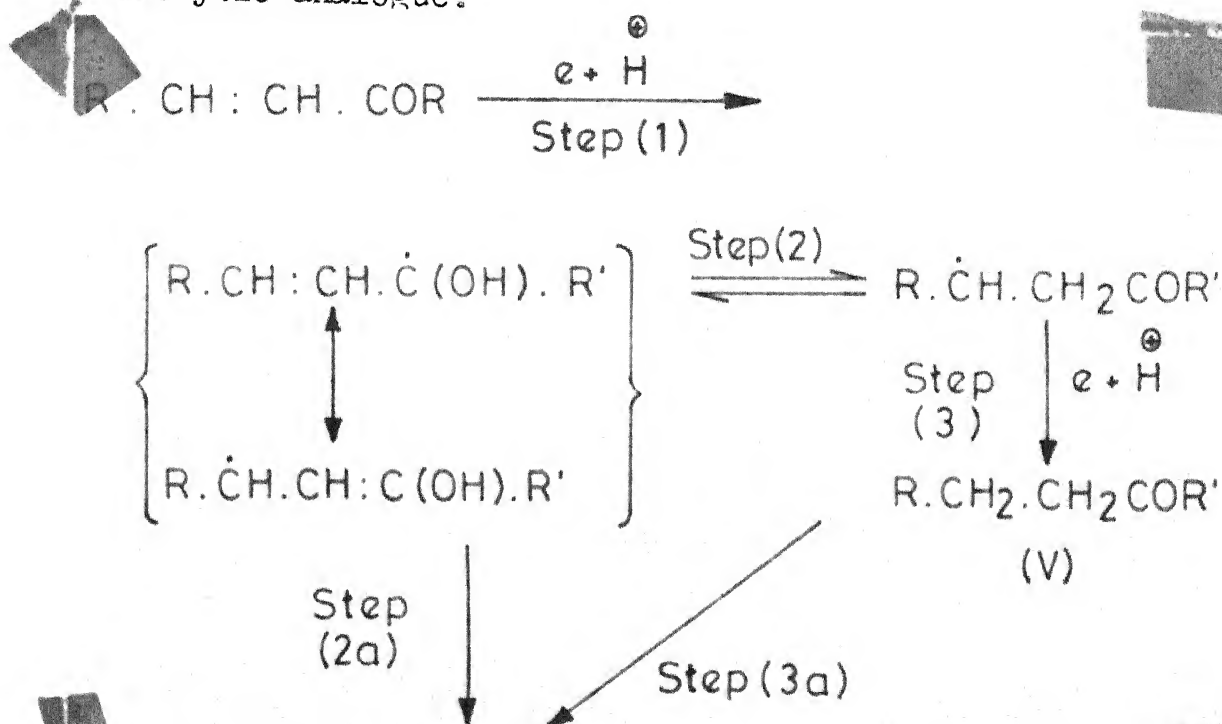
Diphenyl tin hydride<sup>33-35</sup> brings about the reduction of chalcone to yield phenyl styryl carbinol (75%). The distinctive feature of the reaction is that the two hydrogen atoms undergo uncatalysed selective transfer from tin to the carbonyl group of chalcone to give directly the alcohol and no hydrolysis step is required.

1,3-Diphenyl-propan-1-one has been obtained from chalcone by its reaction with diphenyl tin hydride under appropriate conditions. The saturation of the double bond is the net result of two steps.<sup>36</sup> viz., hydrostannation (1,4-addition) and hydrogenolysis. With tributyl tin,<sup>36</sup> however, the reaction does not proceed beyond the hydrostannation stage.

#### Electrolytic Reduction:

Chalcone on electrolytic reduction is reported<sup>37</sup> to yield three products, viz., dibenzylidiacetophenone (35-40%), 1,3,4,6-tetraphenyl-3,4-dihydroxyhexadiene ( ? , 25-30%) and the saturated ketone,  $\text{OCH}_2\text{CH}_2\text{COO}$  (10-15%). The yield of the latter could be raised to 70% by appropriate control of the

reaction conditions. The following mechanism has been proposed<sup>38</sup> for the electrolytic reduction of chalcone and its heterolytic analogue:



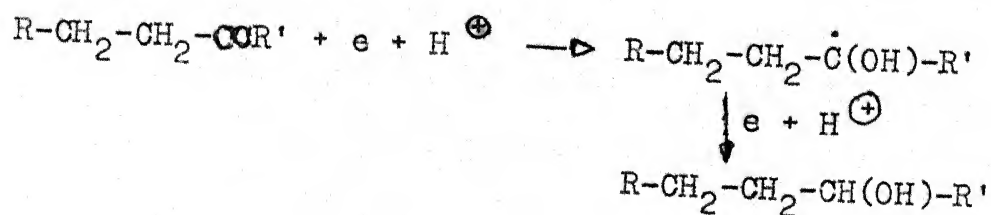
Dimers

(a) R = 2-Quinolylyl; R' = p-MeO-C<sub>6</sub>H<sub>4</sub>

(b) R = R' = Phenyl

(c) R = 2-Furylyl; R' = Phenyl

The ketone (V) can undergo further two one-electron-reduction to yield the corresponding saturated secondary alcohol,<sup>38</sup> thus:



### Meerwein-Ponndorf-Verley Reduction:

Allyl alcohols have been obtained (in 40-70% yield) by the Meerwein-Ponndorf-Verley reduction<sup>39</sup> of chalcones.

A modified method for the Meerwein-Ponndorf-Verley reduction of chalcone, involving the use of aluminium isopropoxide and isopropyl alcohol, has been reported.<sup>40</sup> The removal of acetone from the reaction mixture is unnecessary. The product, 1,3-diphenyl-2-propen-1-ol is obtained in good yield (76%).

### Reduction by Metals:

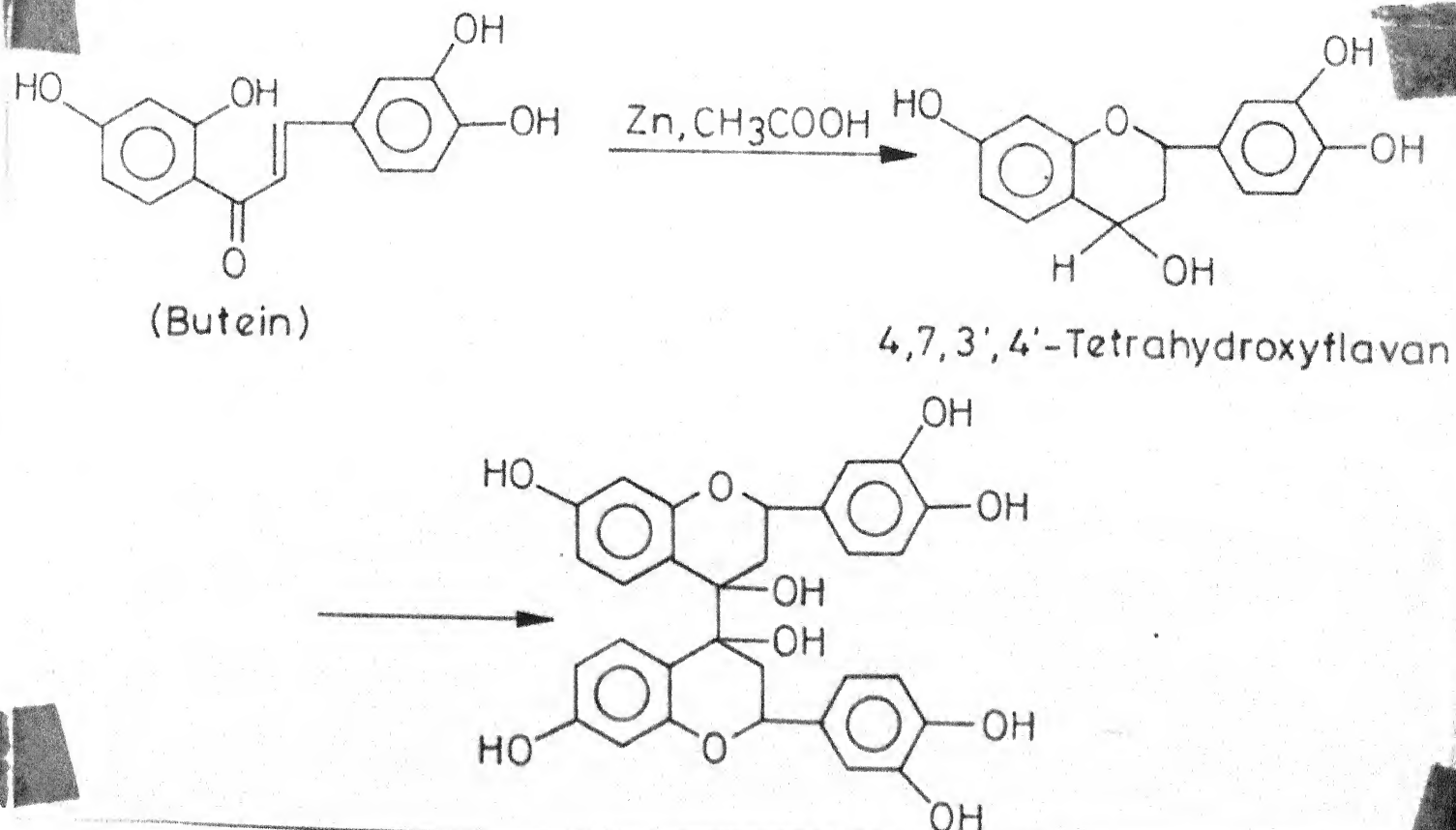
Lithium amalgam<sup>41</sup> brings about the reduction of chalcone giving rise to a small amount of the corresponding alcohol (b.p. 168-71°). The reaction of chalcone with ammonium amalgam is not a clean one, and several products have been isolated.<sup>54</sup> The following are the products that are formed: 1,3,4,6-tetraphenyl-hexan -1,6-dione; 1,3,4,6-tetraphenyl-3,4-dihydroxy-1,5-hexadiene; 1,2,4,5-tetraphenyl cyclohexan-1,2-diol; 1,3-diphenylpropyl alcohol and 1-amino-1, 3-diphenyl-3-propanol.

Benzyl acetophenone is obtained from chalcone when the latter is treated with sodium<sup>42</sup> in alcohol.

1,3,4,6-Tetraphenylhexan -1,6-dione<sup>42</sup> is produced when chalcone is reduced as in Clemmensen reaction or treated with zinc mercury in acetic acid.



2-Hydroxy-3,4-dimethoxy-3',4'-methylenedioxychalcone on reduction with zinc in ethyl alcohol-acetic acid gives amorphous 4-hydroxy-7,8,4'-trimethoxyflavan.<sup>38</sup> Under the same reaction conditions butein yields the corresponding flavan or the pinacol<sup>43</sup>:



Chalcone,<sup>44</sup> on the other hand yields dibenzylidiacetophenone (m.p. 196°) and an isomer (m.p. 269°). Chalcone is reported to undergo reduction by vanadous and chromous salts with the formation of bimolecular products.<sup>45</sup> For example:



### Willgerodt-Kindler Reaction<sup>46</sup>:

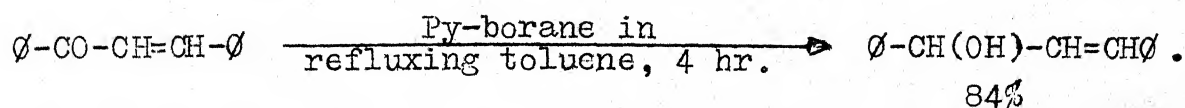
Dihydrochalcone (40%) has been obtained by heating chalcone with sulphur at 115° in the presence of quinoline. Besides the dihydrochalcone; 1,3-diphenylprop-1-ene is also formed, when the above reaction is carried out at a higher temperature (145°). Reduction of olefinic bond in the Willgerodt-Kindler reaction has also been observed in the case of 4-chlorochalcone. However, according to a recent report,<sup>67</sup> cinnamic acid is produced when chalcone is heated in morpholine in presence of sulphur.

### Reduction by 'Hantzsch Ester':

The activated double bond of chalcone is selectively reduced,<sup>47</sup> by 'Hantzsch ester' (diethyl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate) to yield benzylacetophenone and illustrates a case of homogeneous hydrogen transfer reaction.

### Reduction by Pyridine-Borane Reagent:

The selective reduction of the carbonyl group in chalcone has been accomplished with pyridine-borane reagent.<sup>48</sup>



### Reduction by Terpenes<sup>49</sup>:

Hydrogenation of the olefinic double bond in chalcone can be effected<sup>49</sup> by the use of terpenes especially phellandrene and limonene, as hydrogen donors. Thus benzyl acetophenone is produced when chalcone and limonene are refluxed in xylene. The same product results when p-chlorochalcone is subjected to the same treatment, using phellandrene as hydrogen donor. Apparently reductive dehalogenation occurs in the latter reaction.

### Miscellaneous Reduction:

The reduction and alkylation in the  $\alpha$ - and  $\beta$ -positions of chalcone in liquid ammonia have been reported.<sup>50,51</sup>

Chalcone has been converted into its corresponding saturated amine (53%) by reductive amination.<sup>52</sup> The reaction can be conducted by introducing hydrogen gas into an aqueous ethanolic ammonia solution containing chalcone and cyanocobalt complex.

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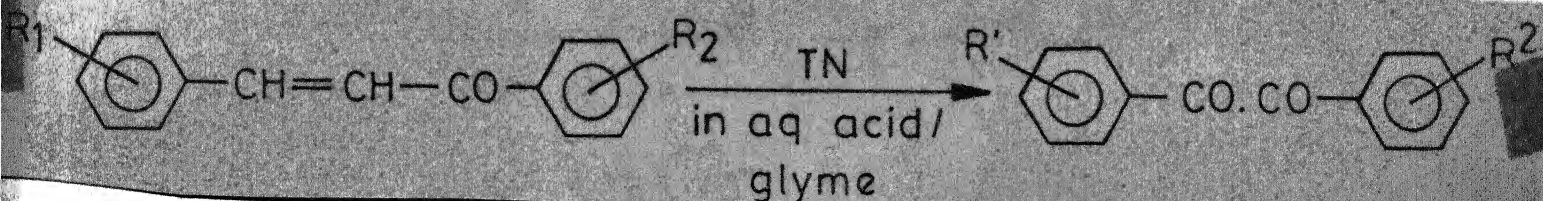
CHAPTER - 4.2

## REACTION OF CHALCONES WITH OXIDIZING AGENTS

Thallic Salts.....	68
Lead Tetraacetate.....	71
Selenium Dioxide.....	72
Manganic Acetate.....	72
Chromic Acid.....	73
Osmium Tetroxide.....	73
Trifluoroperoxyacetic Acid.....	74
Perbenzoic Acid.....	74
Potassium Persulphate.....	75
<u>tert.</u> Butyl Hydroperoxide.....	75
Autoxidation.....	76
Potassium Ferricyanide.....	76
Amine N-Oxides.....	77
References.....	77

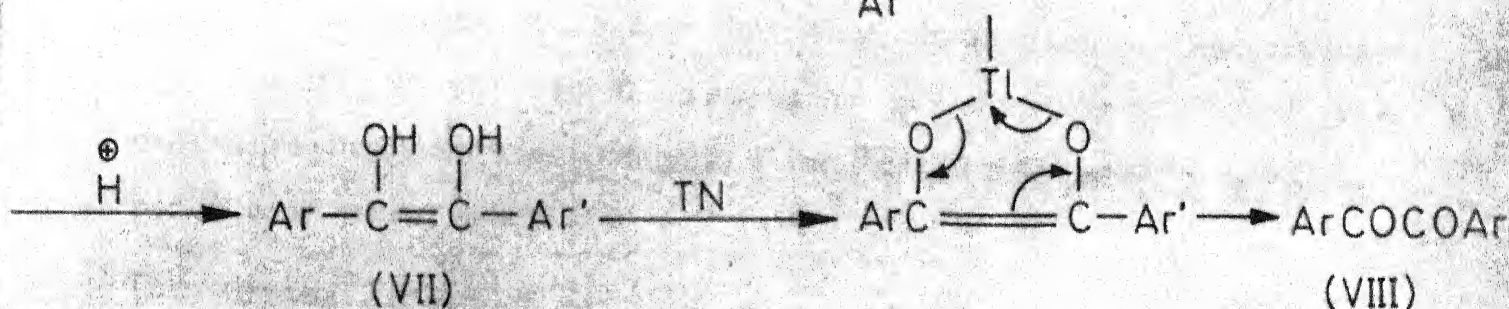
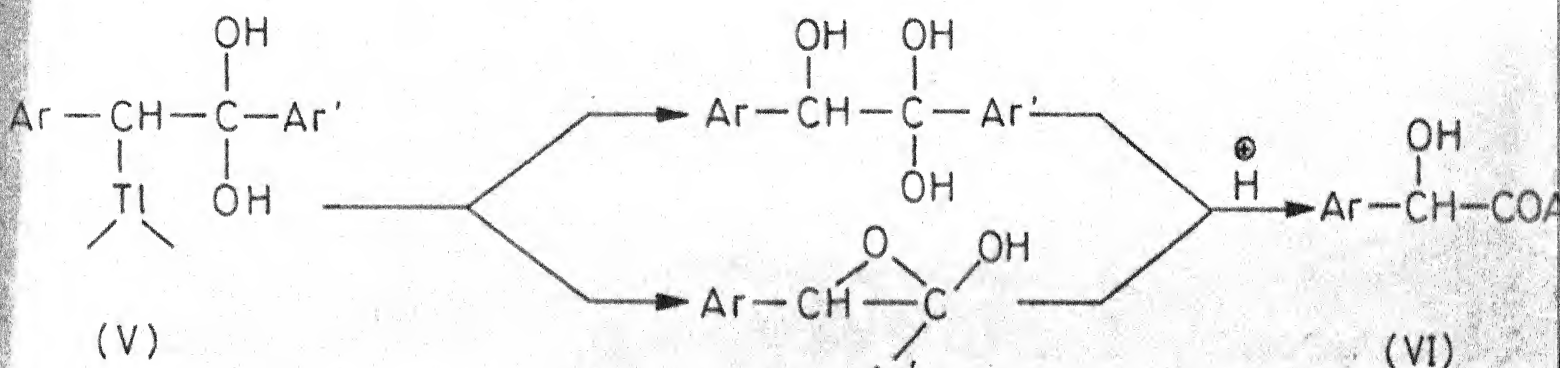
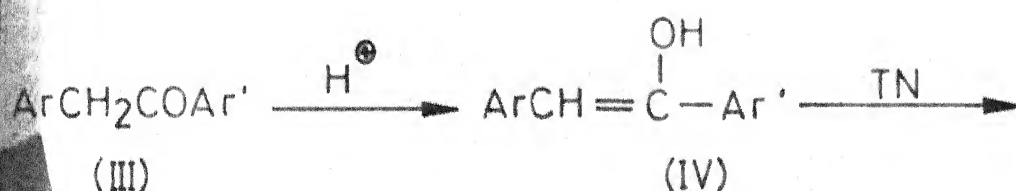
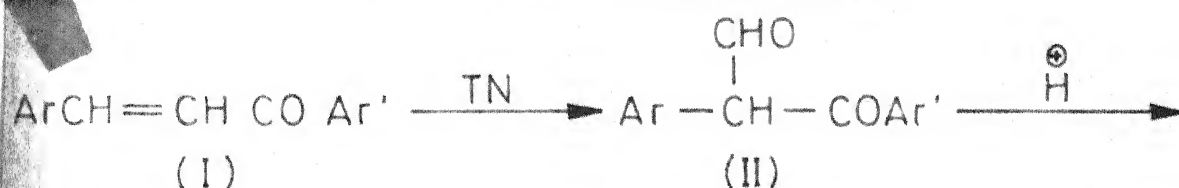
Thallic Salts:

A simple and convenient method for the preparation of symmetrical<sup>1</sup> as well as unsymmetrical<sup>1,2</sup> benzils consists in the oxidation of appropriate chalcones with thallic nitrate<sup>1</sup> (TN):



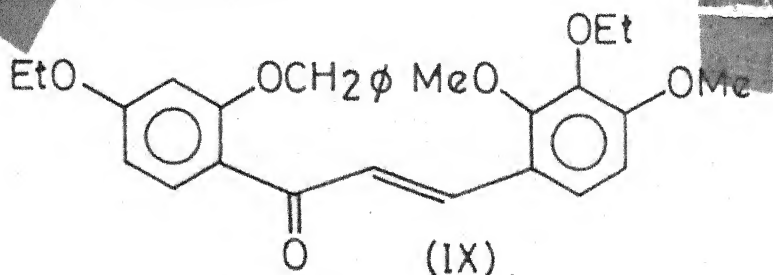
The yield of benzils are in the range of 45-70%. The reaction, however, fails when substituents prone to oxidation (viz. hydroxyl and amino groups) are present, or when both the aromatic rings carry electron withdrawing functions.

The mechanism<sup>1</sup> involved in the thallic nitrate (TN) oxidation of chalcone is shown below:

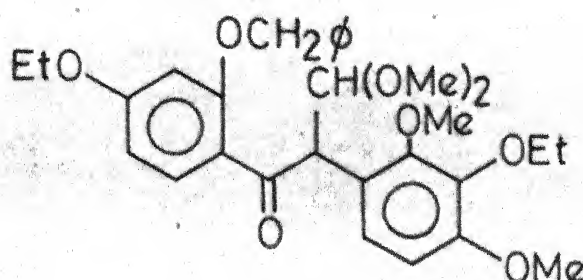


nucleophilic displacement of thallium, leads to the formation of benzoin (VI). (c) Finally, the oxidation of VI gives the benzil (VIII).

If the oxidative rearrangement of chalcone (IX) brought about by thallic salt, is carried out in the presence of methanol, ketoacetal (X) results:



Oxid. Rearrangement,  
100 hr. reflux (MeOH)



The reaction ~~of the intermediate organothallium derivative, followed by its rearrangement.~~<sup>7,9,35,36</sup> This reaction has been exploited for the synthesis of isoflavones.<sup>7,9,35,36</sup> For example, (X) after treatment with methanolic hydrochloric acid, yielded smoothly 3',7-diethoxy-2',4'-dimethoxyisoflavone.<sup>7</sup>

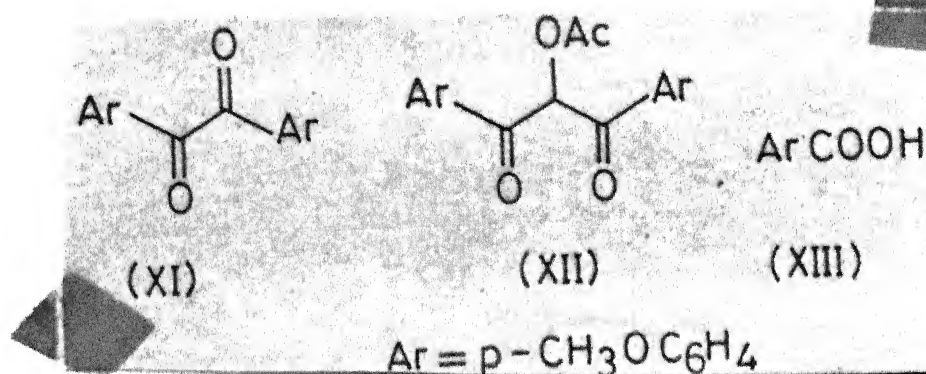
2'-Hydroxychalcones have also been shown<sup>10</sup> to undergo oxidative rearrangement (vide supra) with thallic salts to yield finally the corresponding isoflavones.<sup>10</sup> The syntheses of

several naturally occurring isoflavones<sup>11-13</sup> and related compounds are based on the aforesaid reaction.

The kinetics of thallic acetate oxidation of chalcone has been studied.<sup>14</sup>

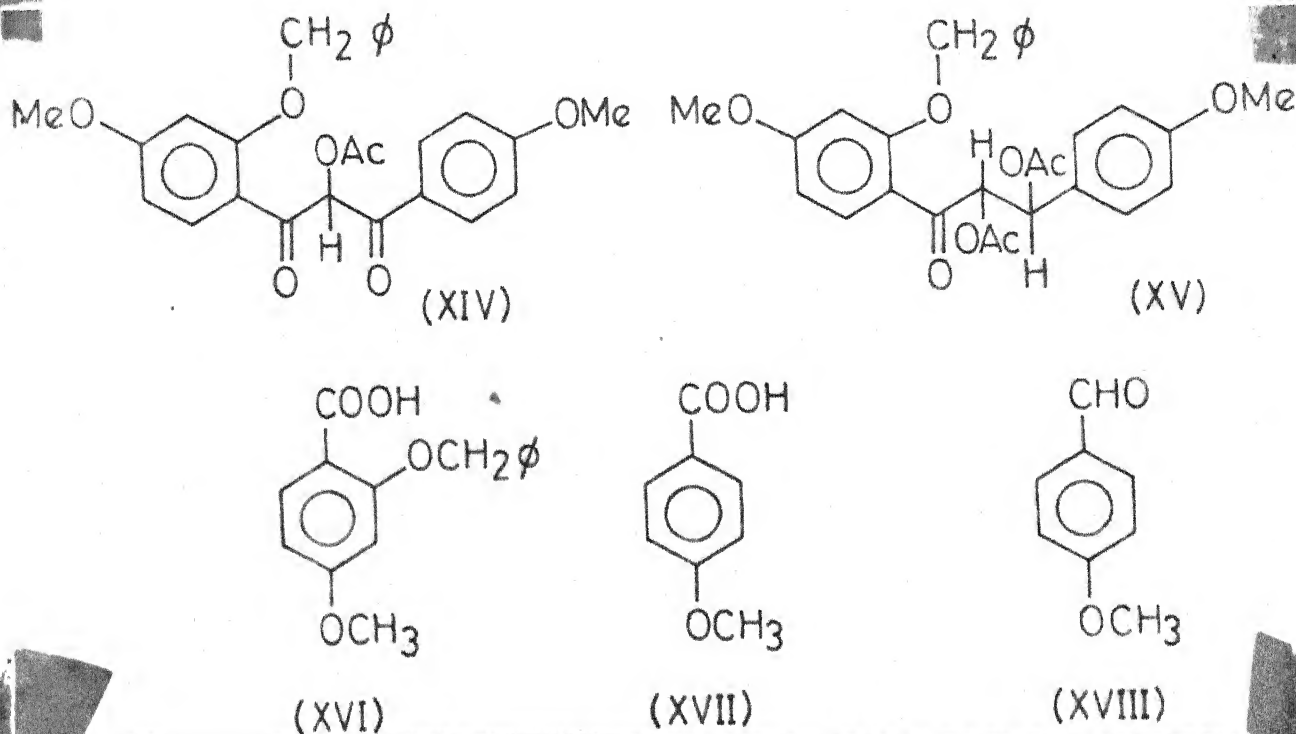
#### Lead Tetraacetate:

The  $\beta$ -hydroxy-chalcones on oxidation with lead tetraacetate<sup>15</sup> give the corresponding benzils together with aromatic acids. In the case of 4,4'-dimethoxy- $\beta$ -hydroxy-chalcone, however, the formation of three products (XI-XIII) is reported.<sup>15</sup>



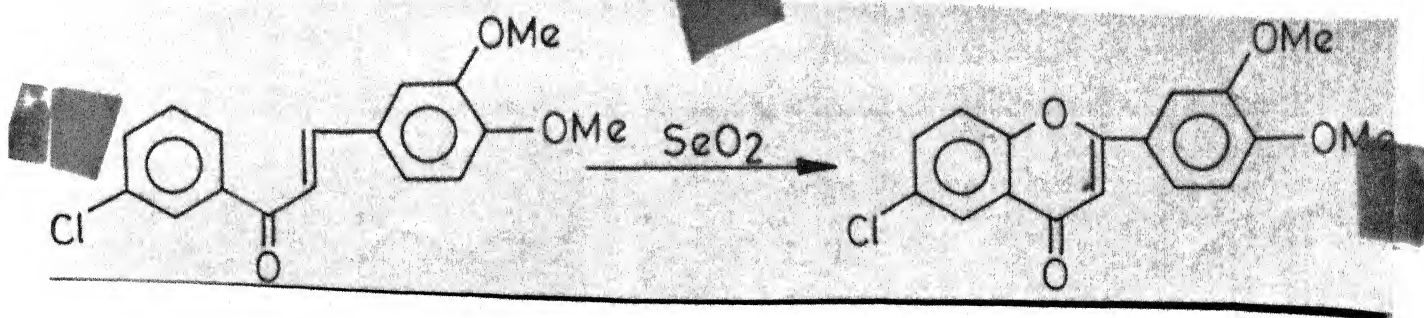
Lead tetraacetate oxidation of 2'-hydroxychalcones,<sup>16</sup> however, yield cis- and trans-aurones, substituted cinnamic and benzoic acids. Five products (XIV-XVIII) are obtained when 2'-benzyloxy-4,4'-dimethoxychalcone is oxidized by the above oxidant.





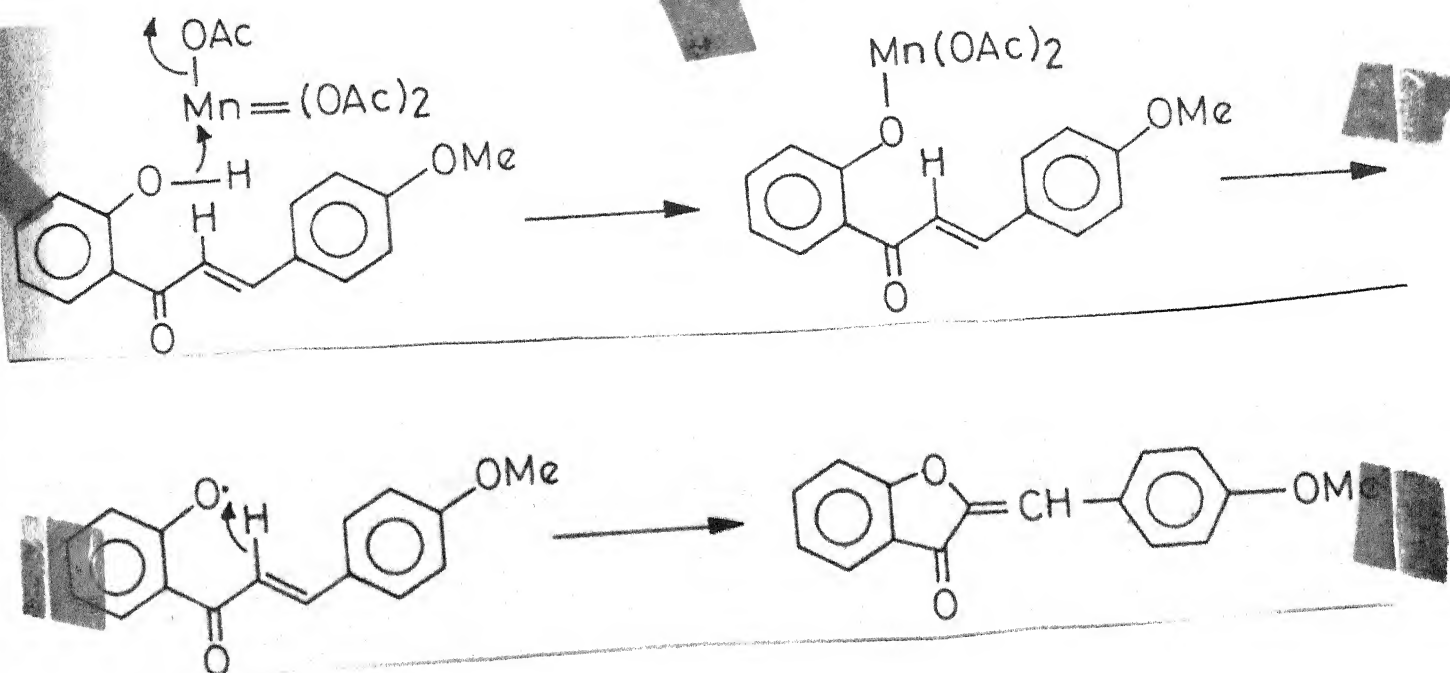
#### Selenium Dioxide:

Chalcones are oxidized smoothly with selenium dioxide to the flavones.<sup>17-19</sup> The following serves as an example<sup>17</sup> for such a transformation:<sup>19</sup>



#### Manganic Acetate:

Fairly good yields of aurones<sup>16,20</sup> are obtainable from 2'-hydroxychalcones by oxidation with manganic acetate in acetic acid. The mechanism of the reaction is outlined as follows<sup>20</sup>:



#### Chromic Acid:

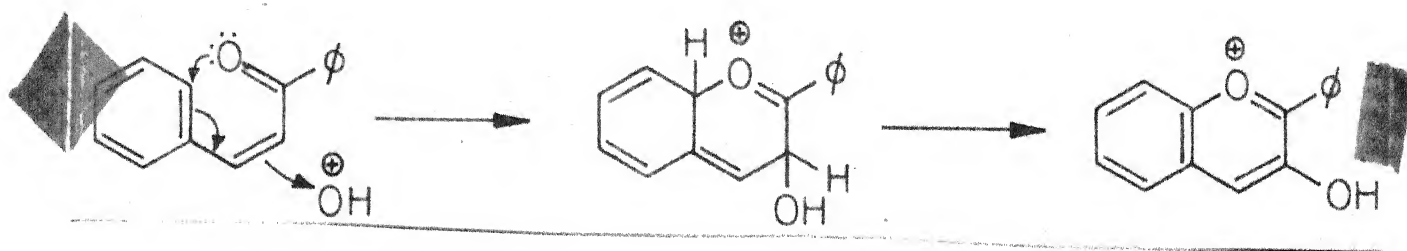
Epoxidation takes place when chalcone and its derivatives are treated with chromic acid.<sup>21</sup> The kinetics of this reaction has been studied.<sup>21</sup> The reaction is reported<sup>21</sup> to involve the electrophilic attack by chromic acid at the olefinic centre of chalcone molecule, resulting in the formation of an epoxide.

#### Osmium Tetroxide<sup>22</sup>:

Chalcone and osmium tetroxide react in ether solution to give a monoester,  $C_{15}H_{12}O_5Os$  in 64% yield.

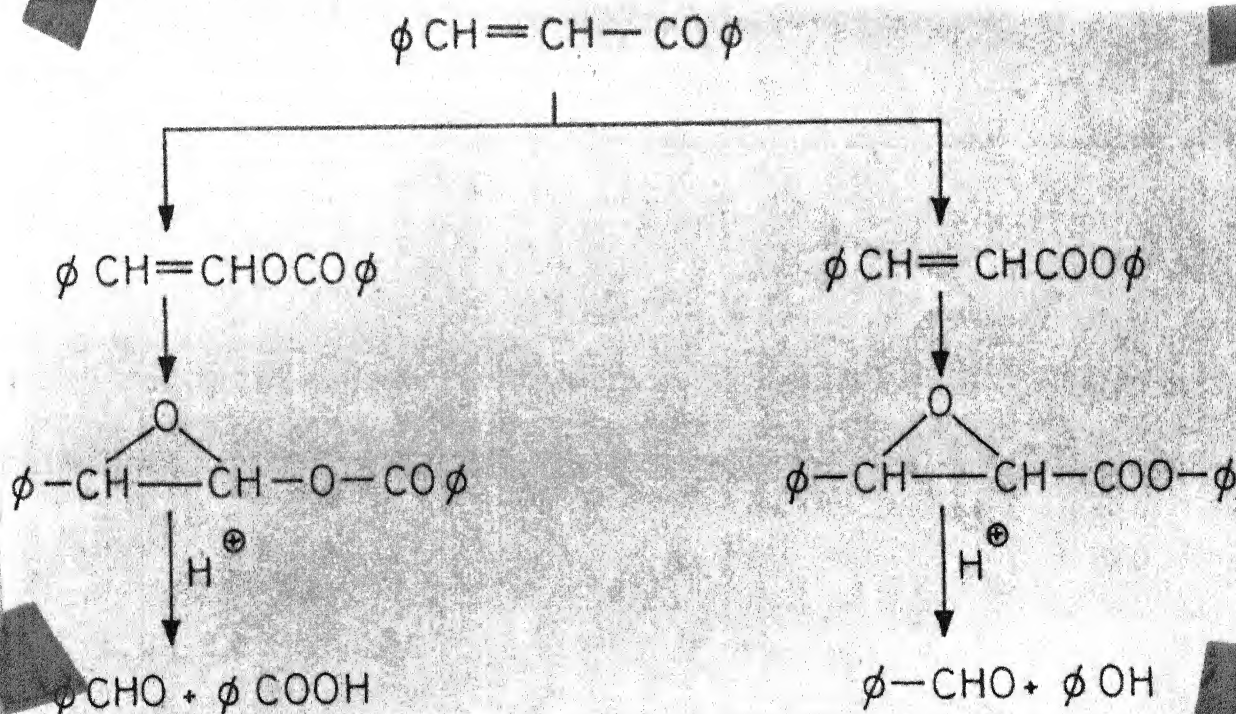
### Trifluoroperoxyacetic Acid:

Oxidative cyclisation of chalcones to flavylium salts have been achieved by the use of trifluoroperoxyacetic acid<sup>23</sup> in methylene chloride. The reagent serves as an electrophilic hydroxylating<sup>24</sup> system. A plausible mechanism<sup>23</sup> for this reaction is given:



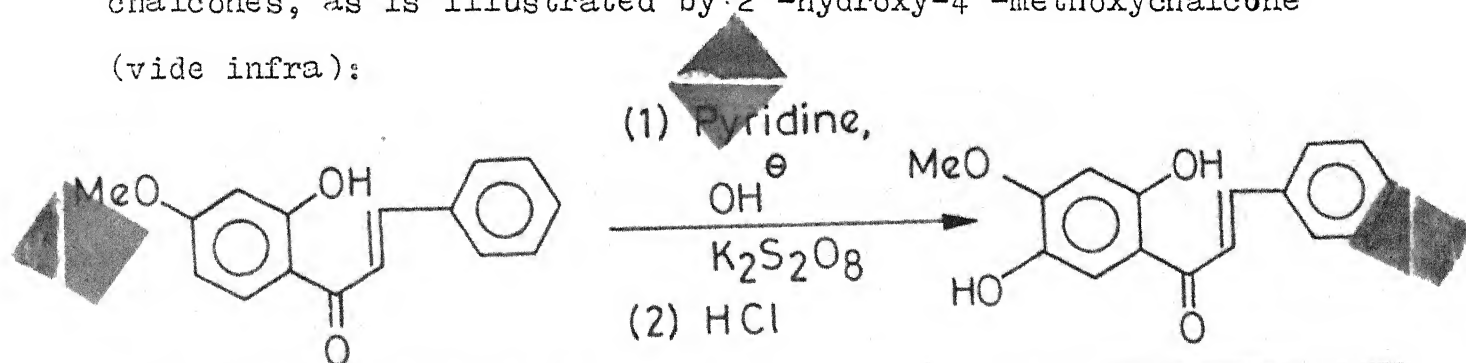
### Perbenzoic Acid:

The reaction of perbenzoic acid with chalcone has been studied.<sup>25</sup> The oxidation of chalcone is considered<sup>26</sup> to proceed through the intermediate formation of epoxy-esters, as follows:

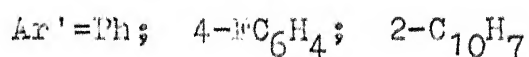
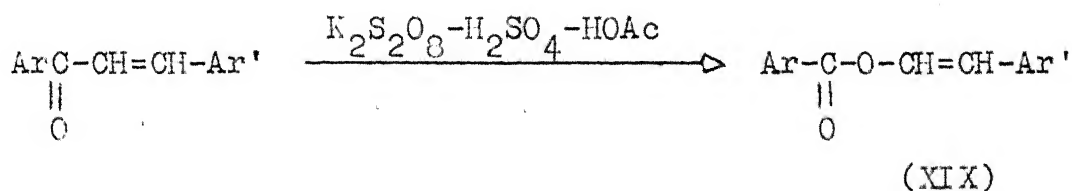


### Potassium Persulphate:

Potassium persulphate, under appropriate experimental conditions is reported<sup>27</sup> to cause the nuclear oxidation of hydroxy-chalcones, as is illustrated by 2'-hydroxy-4'-methoxychalcone (vide infra):

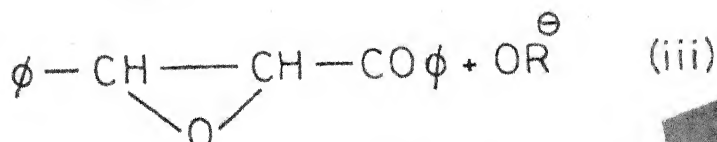
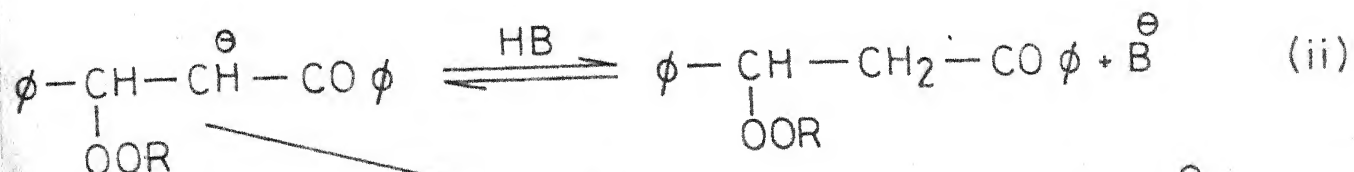


Some trans 1-aryl-2-aryloxy ethylenes (XIX) have been secured<sup>28</sup> by the persulphate oxidation of chalcone and naphthalene analogue of chalcone:



### tert-Butyl Hydroperoxide:

Chalcone is reported to undergo epoxidation when treated with tert-butyl hydroperoxide<sup>29</sup> in the presence of triton-B. With this reagent it is possible to carry out the reaction in a completely homogeneous non-polar medium. The mechanism<sup>29</sup> involved in epoxidation is depicted below:



The equilibrium concentration of the carbanion is sufficiently large to enable step (iii) to compete with the protonation step (ii). Since the elimination step is irreversible, therefore, the reaction is driven in the direction of epoxide formation.

Epoxidation of chalcones has also been achieved by using monoperphthalic acid,<sup>30</sup> as well as by hydrogen peroxide in alkaline medium.<sup>31,32</sup> (see under AFO reaction). The latter method has been extended to the preparation of heterocyclic epoxychalcones.<sup>32</sup>

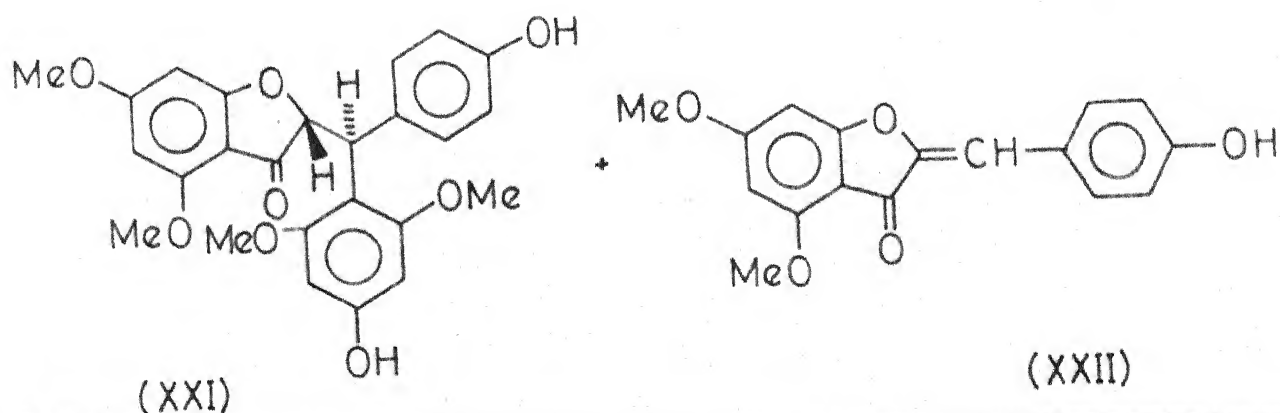
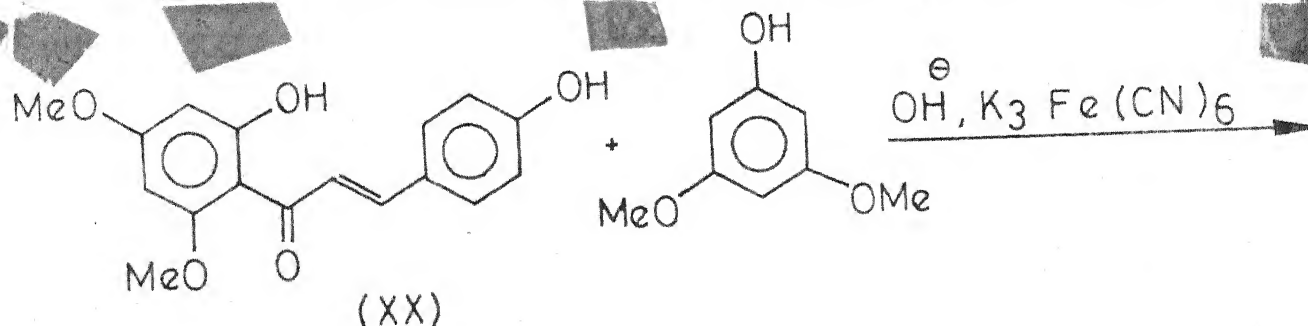
#### Autoxidation:

Chalcone is autoxidized<sup>33</sup> very slowly, in presence of potassium tert. butoxide-tert. butyl alcohol, to two equivalents of benzoic acid (75%).

#### Potassium Ferricyanide:

2',4-Dihydroxy-4',6'-dimethoxychalcone (XX) is reported<sup>34</sup> to undergo oxidative phenol coupling at the  $\beta$ -position to yield

a diastereoisomeric mixture of benzofuranones, XXI (25.5%) and



#### Amine N-oxides.

Flavones have been prepared<sup>37</sup> from 2'-hydroxychalcones by their oxidation with amine N-oxides, viz., pyridine oxide and triethylamine oxide, in the presence of a catalyst.

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CHAPTER - 4.3

## REACTION OF CHALCONES WITH KETONES

Isopropyl and Isobutylketones.....	81
Acetophenones.....	82
Benzophenone.....	82
Phenyl benzyl ketone.....	83
Cyclopentanone.....	83
3-Methylcyclohexanone.....	84
Tetraphenylcyclopentadienone.....	84
Menthone.....	84
Fenchone and Camphor.....	85
Flavanones.....	85
2-Substituted 5,6-benzochromanone.....	86
Acetylacetone.....	86
Dihydroresorcinol.....	87
5,5-Dimethylcyclohexandione.....	87
2-Nitro-1,3-Indandione.....	88
Benzylidene <u>bis</u> (acetophenone).....	88
1,3,5-Triphenylpentan -1,5-dione.....	88
References.....	88

Isopropyl and Isobutyl Ketones:

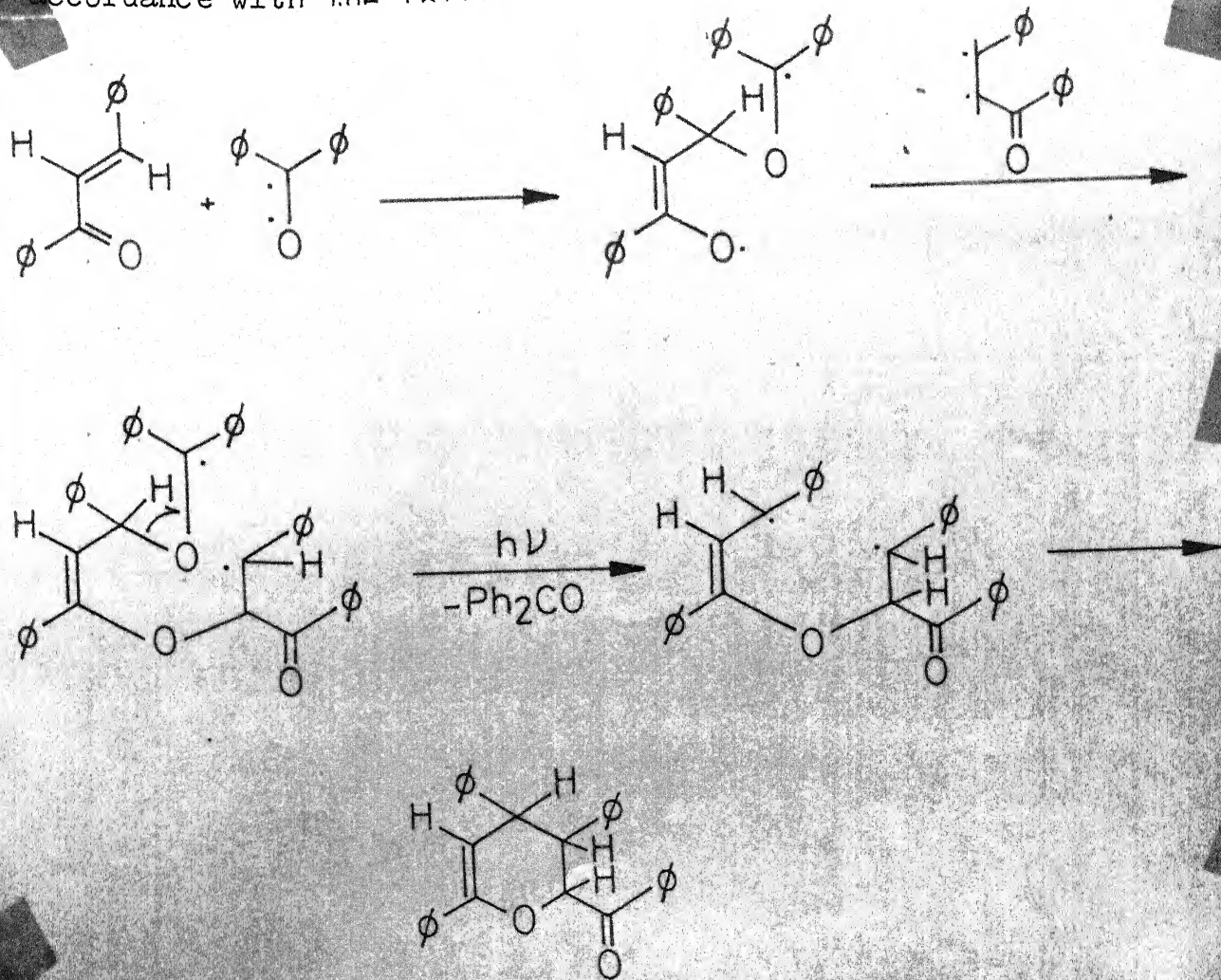
Several diketones, as erythro-threo mixtures, have been prepared<sup>1</sup> by the reaction of chalcones with enolates derived from isopropyl and isobutyl ketones.

Acetophenones:

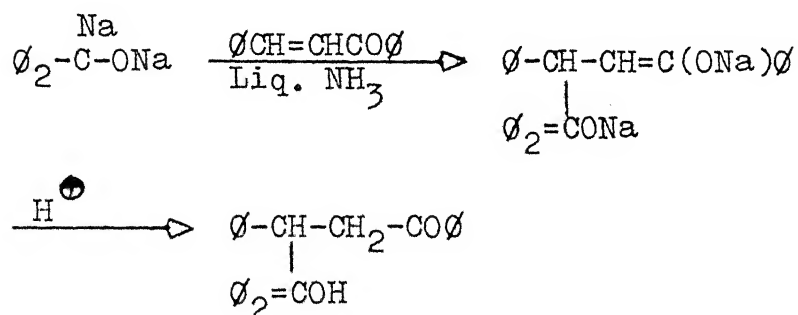
Chalcone is reported<sup>2</sup> to undergo 1,2- or 1,4-addition with the ketone enolates, depending upon the conditions of experiment. Chalcone and MeO-CH<sub>2</sub>COPh cyclised with ammonium acetate-acetic acid to yield 2,4,6-triphenyl pyridine<sup>3</sup>. Chalcone-LAH complex in ether solution is reported<sup>4</sup> to react with acetophenone to yield 2,3,5-triphenylpentan-2,5-diol.

Benzophenone:

The benzophenone-sensitized irradiation of chalcone furnishes 2-benzoyl-3,4,6-triphenyl-1,2,3-dihydropyran<sup>5</sup> (I) in accordance with the following:

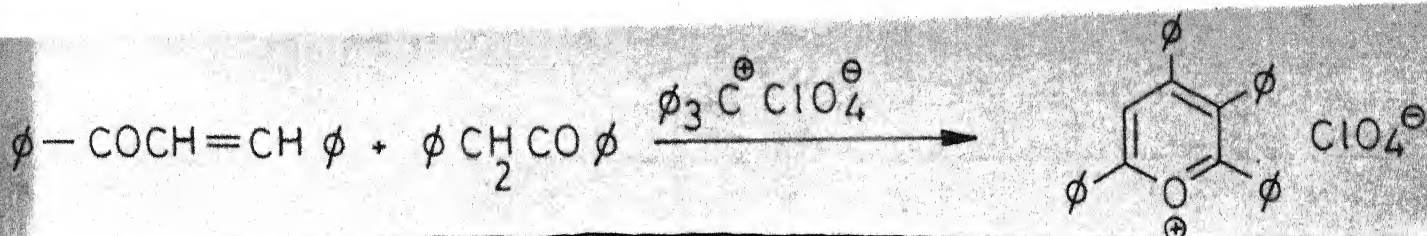


Disodiobenzophenone salt is reported<sup>6</sup> to react with chalcone to form, after acidification, the keto alcohol, viz.,  $\beta, \gamma, \gamma$ -triphenyl- $\gamma$ -hydroxybutyrophenone, in 47% yield.



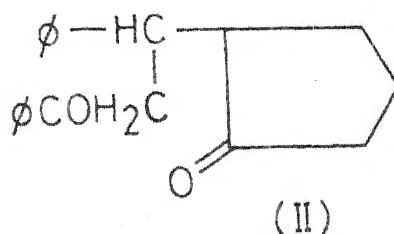
#### Phenyl Benzyl Ketone<sup>7</sup>:

A quantitative yield of the Michael adduct is obtained when 4'-methylchalcone is treated with phenylbenzyl ketone under alkaline conditions. However, a pyrylium salt<sup>8</sup> is produced, if triphenylmethyl perchlorate is used in the aforesaid reaction. Thus



#### Cyclopentanone<sup>9-12</sup>:

Under the influence of diethylamine or piperidine, chalcone reacts with cyclopentanone yielding a semicyclic-1,5-diketone, viz.,  $\alpha$ -benzoyl- $\beta$ -phenyl cyclopentanonylethane<sup>9</sup> (II)



3-Methylcyclohexanone<sup>11,12</sup>:

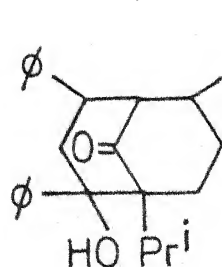
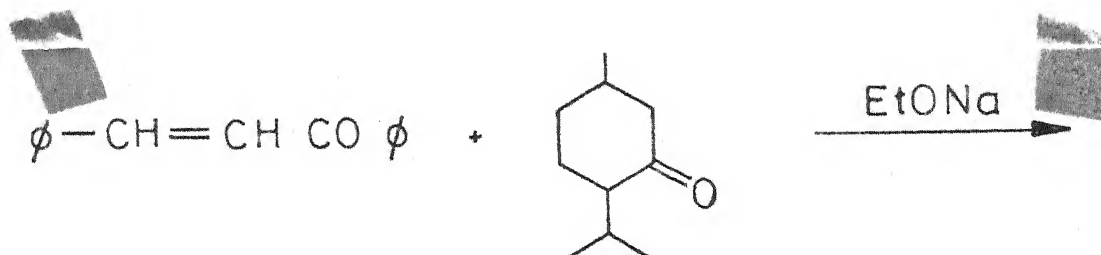
The 1,5-diketone, viz.,  $\alpha$ -benzoyl- $\beta$ -phenyl (3-methyl cyclohexanonyl) ethane, in two stereoisomeric forms is obtained by the reaction of 3-methyl cyclohexanone with chalcone, under appropriate conditions. Michael reaction of chalcone with 2-methylcyclohexanone is also reported.<sup>10</sup>

Tetraphenylcyclopentadienone:

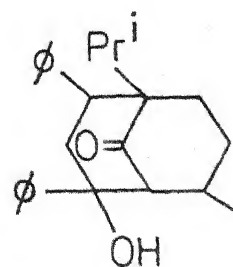
2,3,4,5,6-Pentaphenylbenzophenone<sup>13</sup> results from the reaction of chalcone and tetraphenylcyclopentadienone at an elevated temperature ( $\sim 300^\circ$ ).

Menthone:

A bicyclic ketoalcohol<sup>14</sup> (III) or (IV) result by the interaction of chalcone and menthone in the presence of sodium ethoxide:



(III)



(IV)

2,4 - Diphenyl - 5 ( or 1 ) - isopropyl - 8 ( or 6 )  
methyl 9 - keto - 4 - hydroxybicyclononane

#### Fenchone and Camphor:

Dibenzal triacetophenone<sup>15</sup> is formed when chalcone is reacted with alcoholic sodium hydroxide in the presence of fenchone or camphor.

#### Flavanones<sup>16,17</sup>:

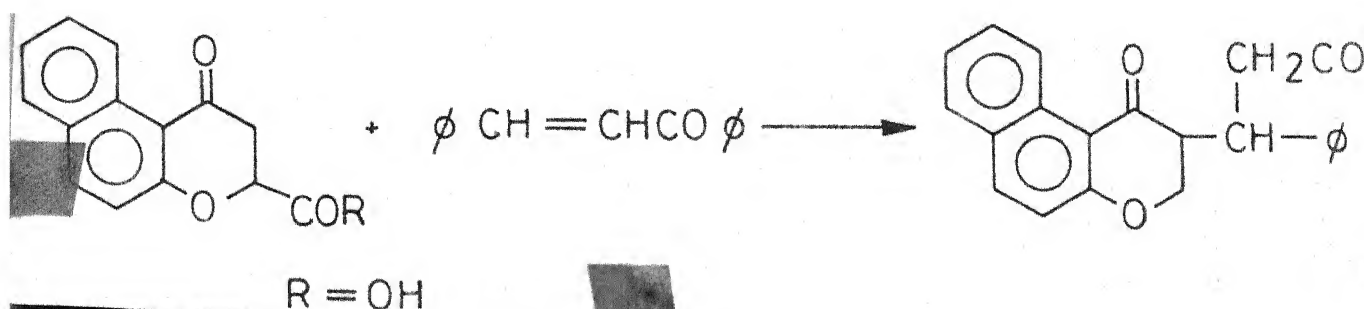
Chalcone and flavanone undergo addition reaction in the presence of a base, viz., sodium amide, sodium or caustic alkali, to yield 2-phenyl-2-phenacyl benzyl 2,3-dihydro-1,4-benzopyrone.

The presence of a 3',4'-methylenedioxy substituent in the chalcone component retards the aforesaid reaction, while a nitro group inhibits the same.<sup>17</sup> A mechanism for the aforesaid reaction has been suggested.<sup>18</sup>



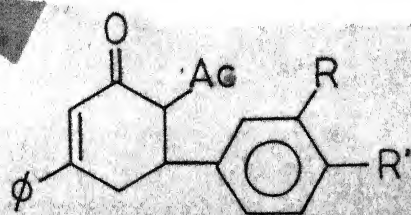
2-Substituted 5,6-benzochromanone:

Michael adducts are formed when chalcone is allowed to react with 2-substituted 5,6-benzochromanone.<sup>19</sup> The following serve as an illustrative example:

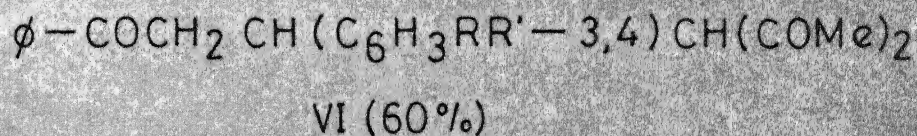


Acetylacetone:

Chalcone reacts with acetyl acetone<sup>20</sup> (at 120°) to yield cyclohexenone derivative (V). When the above reaction is conducted at room temperature, an addition product (VI) is obtained<sup>20</sup>:



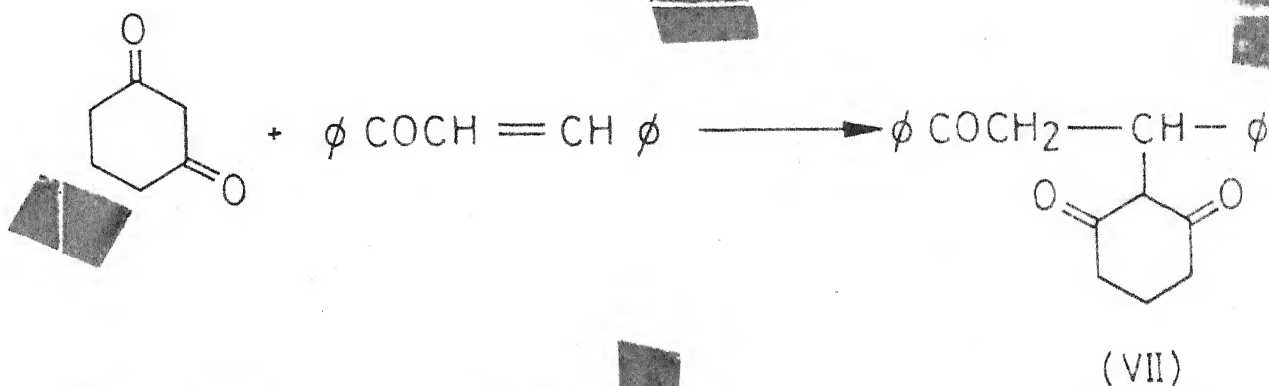
V (40—43%)



[R = R' = H ; R = H ; R' = OMe ; RR' = OCH<sub>2</sub>O]

Dihydroresorcinol<sup>21</sup>:

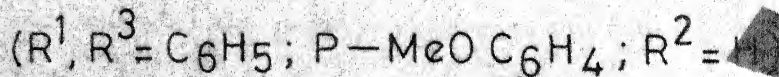
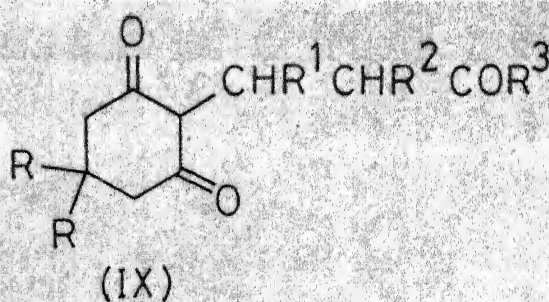
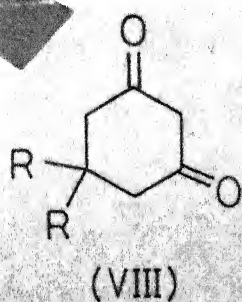
2- [1-Phenyl-2-benzoyl ethyl] cyclohexane 2,6-dione (VII) has been secured



in 58% yield by the reaction of dihydroresorcinol and chalcone.

5,5-Dimethylcyclohexandione:

Condensation of VIII with chalcone or *pp'*-dimethoxychalcone, in the presence of piperidine or sodium ethoxide gave IX<sup>22</sup> in a good yield. Higher yields were obtained with sodium ethoxide catalyst.



2-Nitro-1,3-Indandione:

A good yield (74%) of 1,3-diphenyl-3 (2-nitro-1,3-indandion-2-yl)-1-propanone has been obtained<sup>23</sup> by the interaction of chalcone with 2-nitro-1,3-indandione in hexane.

Benzylidene bis (acetophenone):

The synthesis of pyrylium salt has been achieved<sup>24</sup> by the interaction of benzylidene bis (acetophenone) with chalcone in acetic acid medium, using boron trifluoride as the catalyst.

1,3,5-Triphenylpentan<sup>a</sup>-1,5-dione:

The interaction of 1,3,5-triphenylpentan-1,5-dione and chalcone in presence of perchloric acid results in the formation of pyrylium salt.<sup>25</sup> In this reaction chalcone is reported<sup>25</sup> to act as a hydride ion acceptor.

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(1968).

CHAPTER - 4.4

## REACTION OF CHALCONES WITH ESTERS

Ethyl Acetate.....	91
Ethyl Acetoacetate.....	91
Ethyl Phenylacetate.....	92
Ethyl Benzoylacetate.....	93
Ethyl Cyanoacetate.....	93
Ethyl- $\alpha$ -Cyanobutyrate.....	94
Ethyl Thioglycolate.....	94
Malonic Esters.....	95
Methyl Succinate.....	97
Dimethyl Acetylene Dicarboxylate.....	97
References.....	98

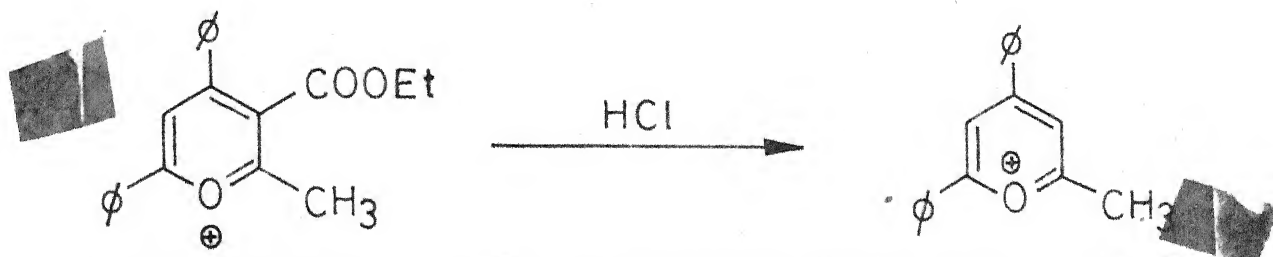
Ethyl Acetate:

Chalcone undergoes a Michael type of reaction with ethyl acetate<sup>1</sup>, in the presence of triphenyl methyl sodium to yield ethyl  $\alpha$ -acetyl  $\beta$ -phenyl- $\gamma$ -benzoyl butyrate (66%).

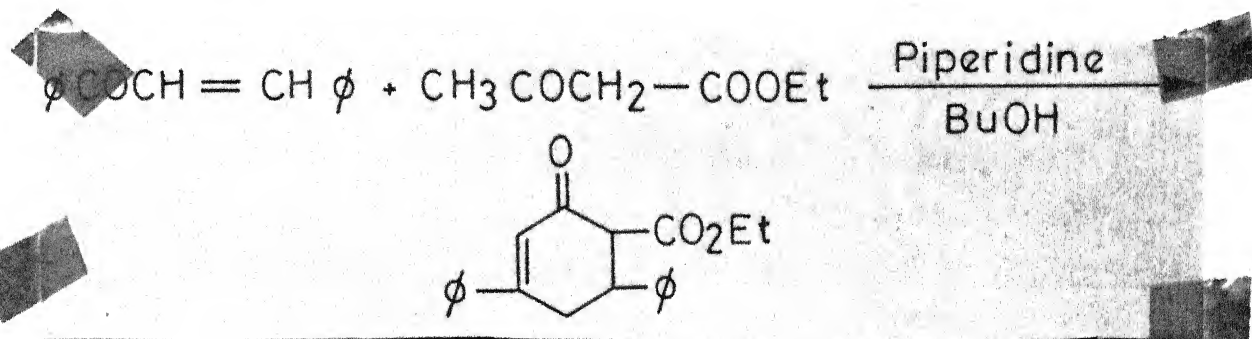
Ethyl Acetoacetate:

Chalcone reacts with ethyl acetoacetate to yield a variety of different compounds, viz., Michael adduct<sup>2</sup>, pyrylium salt<sup>3</sup> or cyclohexanone<sup>4</sup> derivative, depending upon the experimental conditions employed. Thus, in the presence of boron trifluoride

etherate, the above reaction yields the pyrylium salt according to the reaction<sup>3</sup>:



Here the chalcone, beside entering the reaction, also acts as a hydride ion acceptor and gets converted to dihydrochalcone. Chalcone<sup>4</sup> and its derivatives<sup>5-7</sup> undergoes condensation with ethyl acetoacetate to yield the corresponding cyclohexanone derivatives. Example<sup>4,8</sup>:



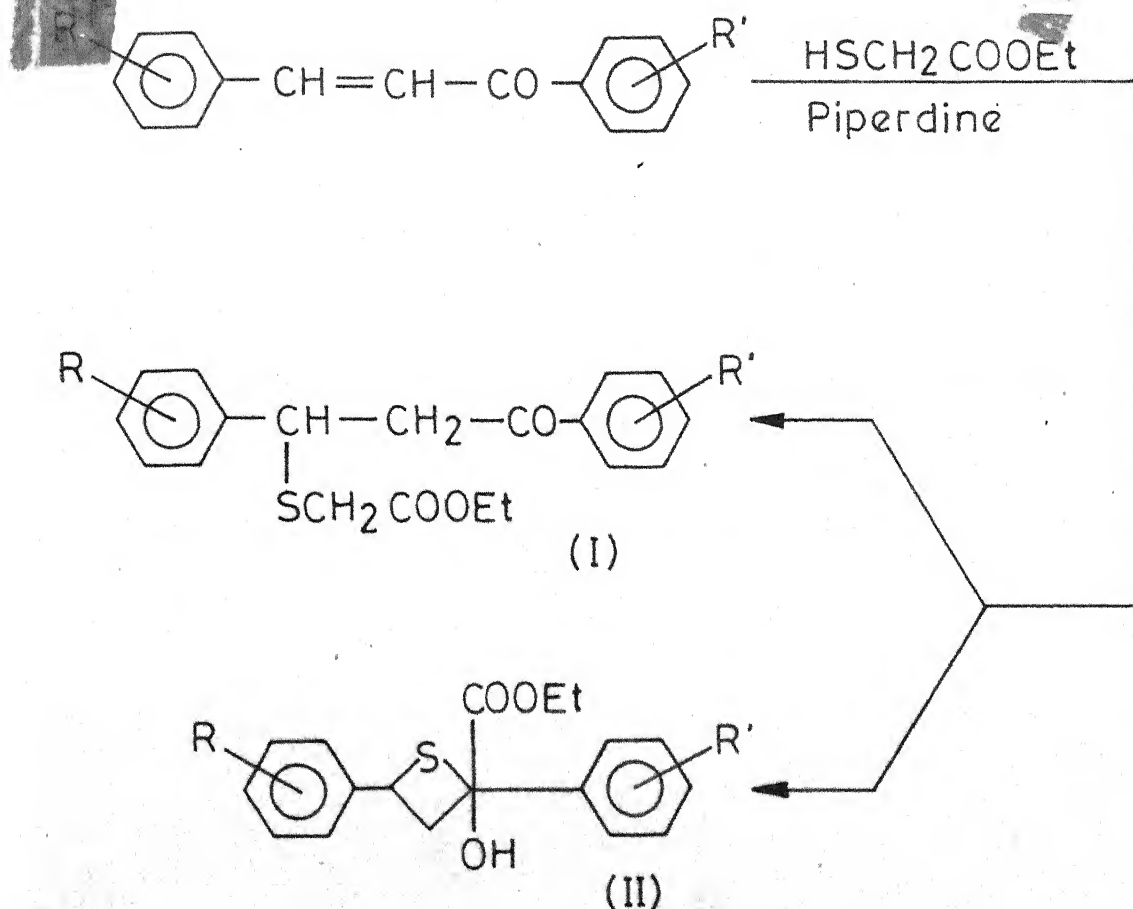
Furan analogue of chalcone<sup>9</sup> also reacts with ethyl acetoacetate in the above manner.

#### Ethyl Phenyl Acetate:

Chalcones-carrying substituents in ring B- have been reacted with ethyl phenyl acetate<sup>10</sup> to yield butyrates of the following type:  $\text{R}'-\text{C}_6\text{H}_4\text{CH}(\text{CH}_2\text{COPh})\text{CHPhCO}_2\text{Et}$ . Under Michael







i)  $R = R' = H$

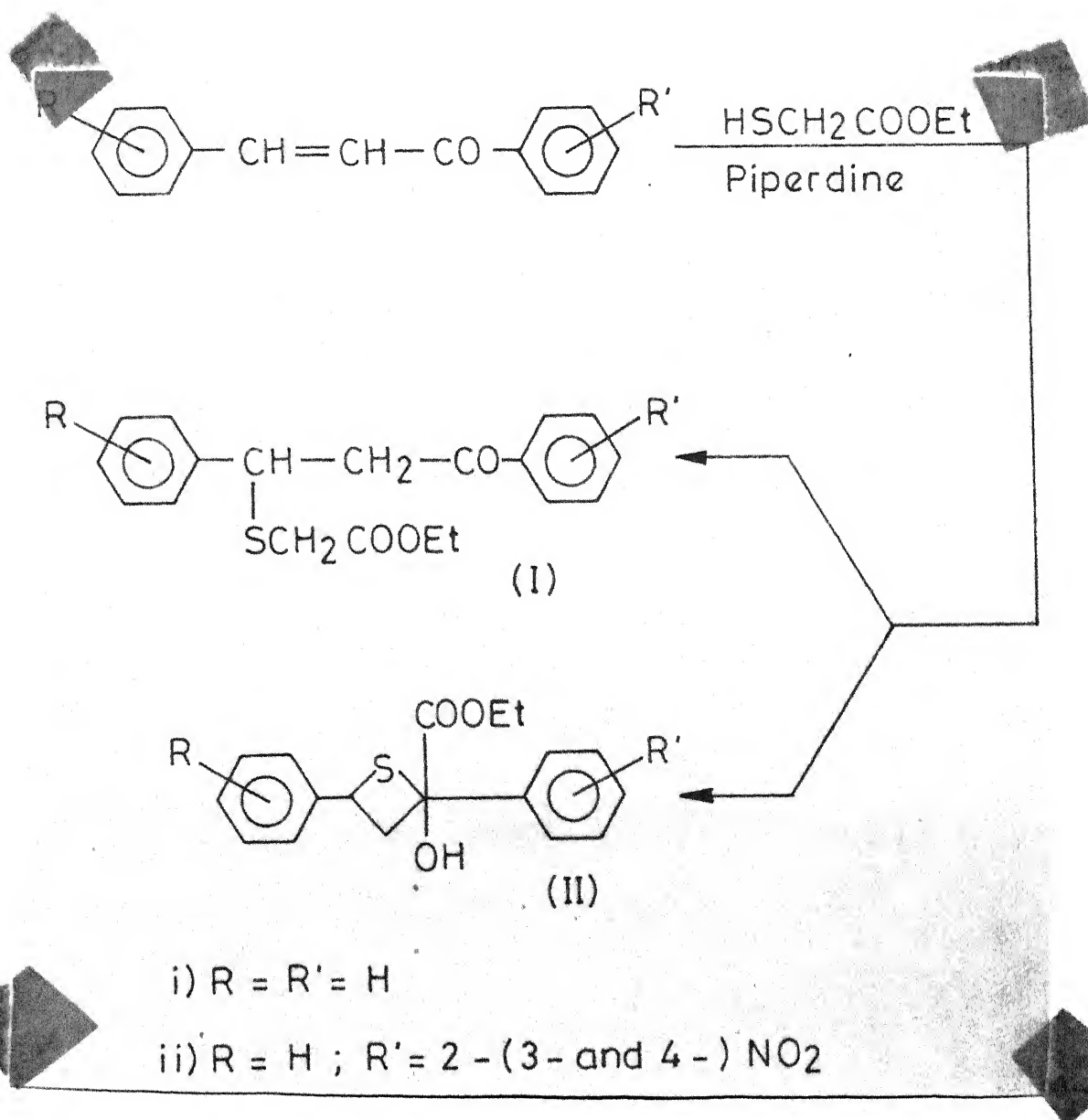
ii)  $R = H$  ;  $R' = 2 - (3 - \text{and } 4 - ) NO_2$ .

#### Ethyl $\alpha$ -cyanobutyrate:

Chalcone undergoes Michael addition when reacted with ethyl  $\alpha$ -cyanobutyrate. The kinetics of this reaction has been investigated.<sup>16</sup>

#### Ethyl Thioglycolate:

Chalcone and nitrochalcones are reported<sup>17</sup> to react with ethyl thioglycolate, in the presence of piperidine, to yield an addition compound (I) and a cyclised product (II).

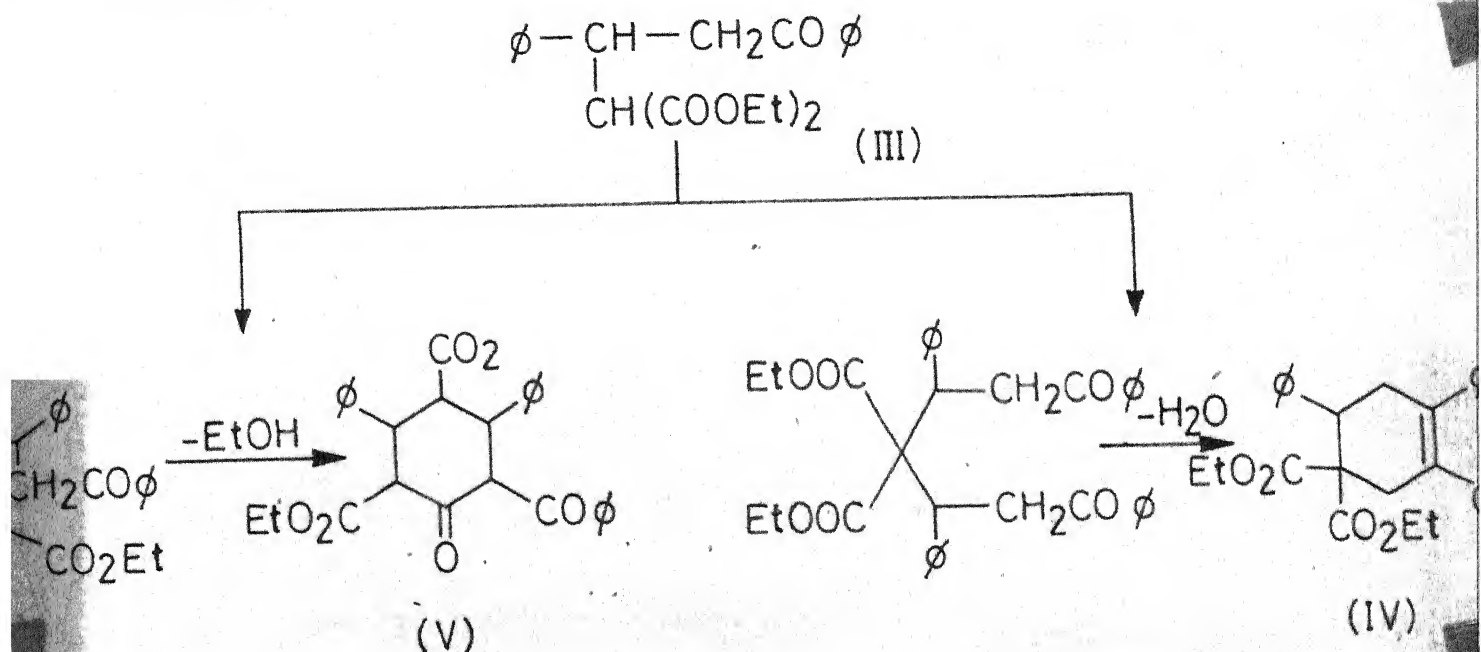


### Malonic Esters:

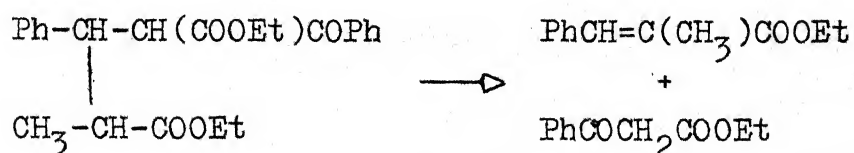
Malonic ester<sup>2,18</sup> undergoes Michael addition with chalcone in the presence of a basic catalyst viz., piperidine. The mechanism of this reaction is reported.<sup>18</sup> Polyfluorochalcones<sup>19</sup> also undergo the above-mentioned reaction, but with difficulty.

Chalcone has been found to react with malonic ester<sup>20</sup> in basic medium (or in the presence of a complex derived from ketal

and potassium hydroxide)<sup>21,22</sup> to yield  $\alpha$ -carbethoxy- $\beta$ -phenyl- $\gamma$ -benzoyl butyric ester<sup>21,23</sup> (III). Depending, however, on the conditions of experiment, other products (IV and V) can also be obtained<sup>23,24</sup>



Methyl malonic ester<sup>25,26</sup> likewise adds to chalcone to yield  $\alpha$ -methyl- $\alpha$ -carbethoxy- $\gamma$ -phenyl- $\gamma$ -benzoylbutyric ester<sup>23</sup> (VI, 80%) with larger concentration of ethoxide (1 molar), however, VI undergoes complete retrogression<sup>23</sup> to yield sodium enol methylmalonic ester (90%), chalcone and traces of benzoyl acetic ester. Butyric ester VI, obtained as above, but in the presence of piperidine, undergoes further reaction as illustrated<sup>26</sup>:

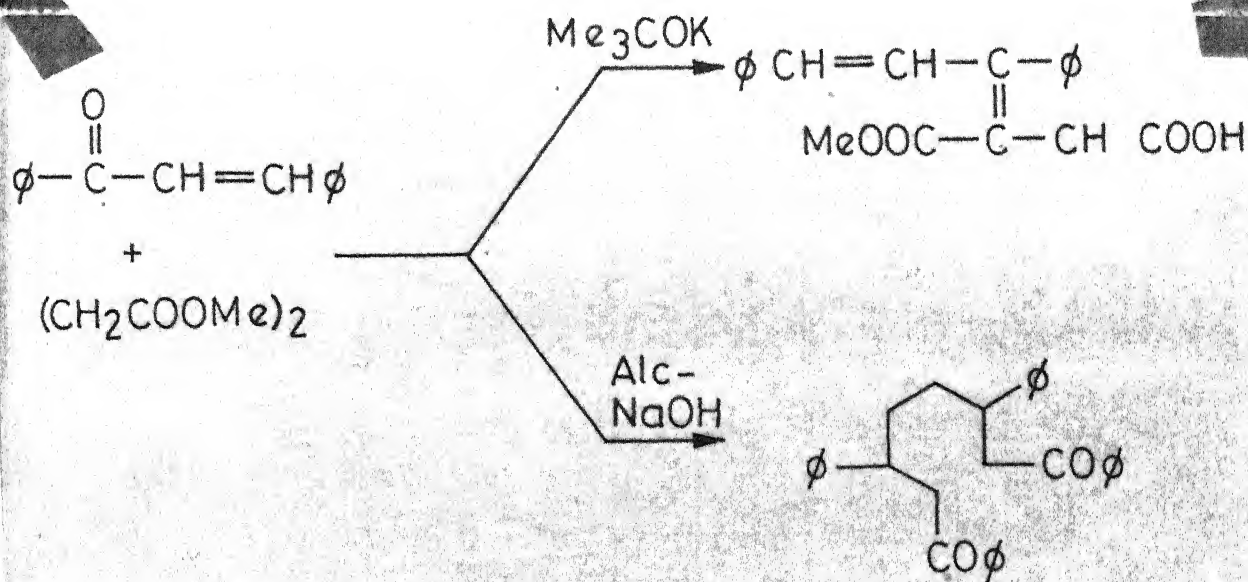


Ethyl alkyl malonate<sup>27</sup> and chalcone undergo Michael condensation to give the product (alkyl =  $\text{CH}_3$ ; 80%). In the

other case (alkyl = ethyl) the expected Michael condensation product is not isolable. This has been attributed<sup>27</sup> to steric hindrance as well as to the instability of the Michael addition product towards sodium ethoxide present in the reaction medium.

### Methyl Succinate:

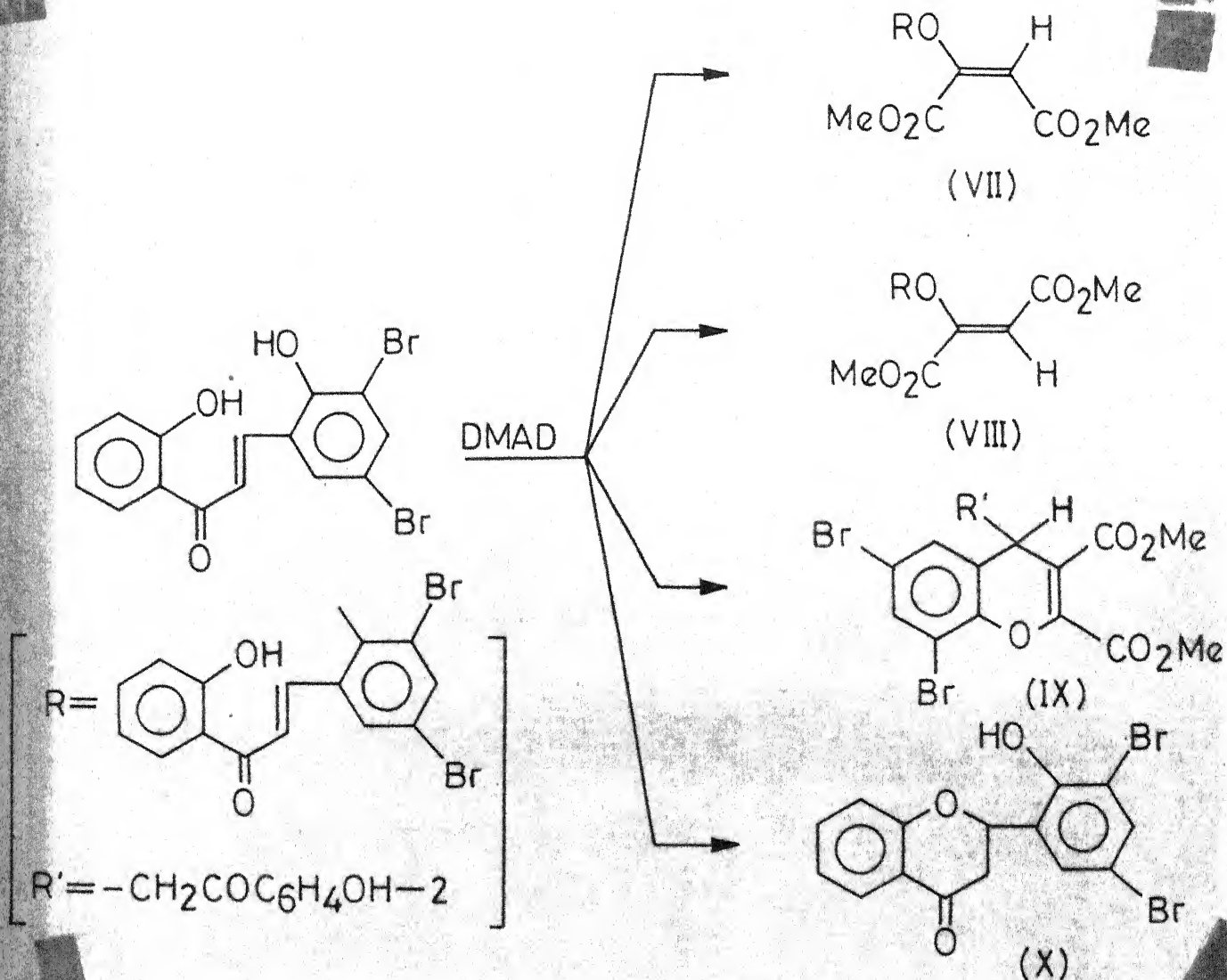
Methyl succinate reacts with chalcone yielding different products<sup>7,12</sup> depending upon the reaction conditions. Thus:



### 1,3,6,8-Tetraphenyl-1,8-octandione

### Dimethyl Acetylene Dicarboxylate<sup>28</sup>:

2-Hydroxychalcone and 2,2'-dihydroxychalcone react with dimethyl acetylene dicarboxylate (DMAD) to give a mixture of phenoxymaleates (VII), phenoxyfumarates (VIII) and some cyclic products, viz., chromenes (IX) and or flavanones (X). The reaction of 3,5-dibromo-2,2'-dihydroxychalcone with DMAD is typical and is illustrated:



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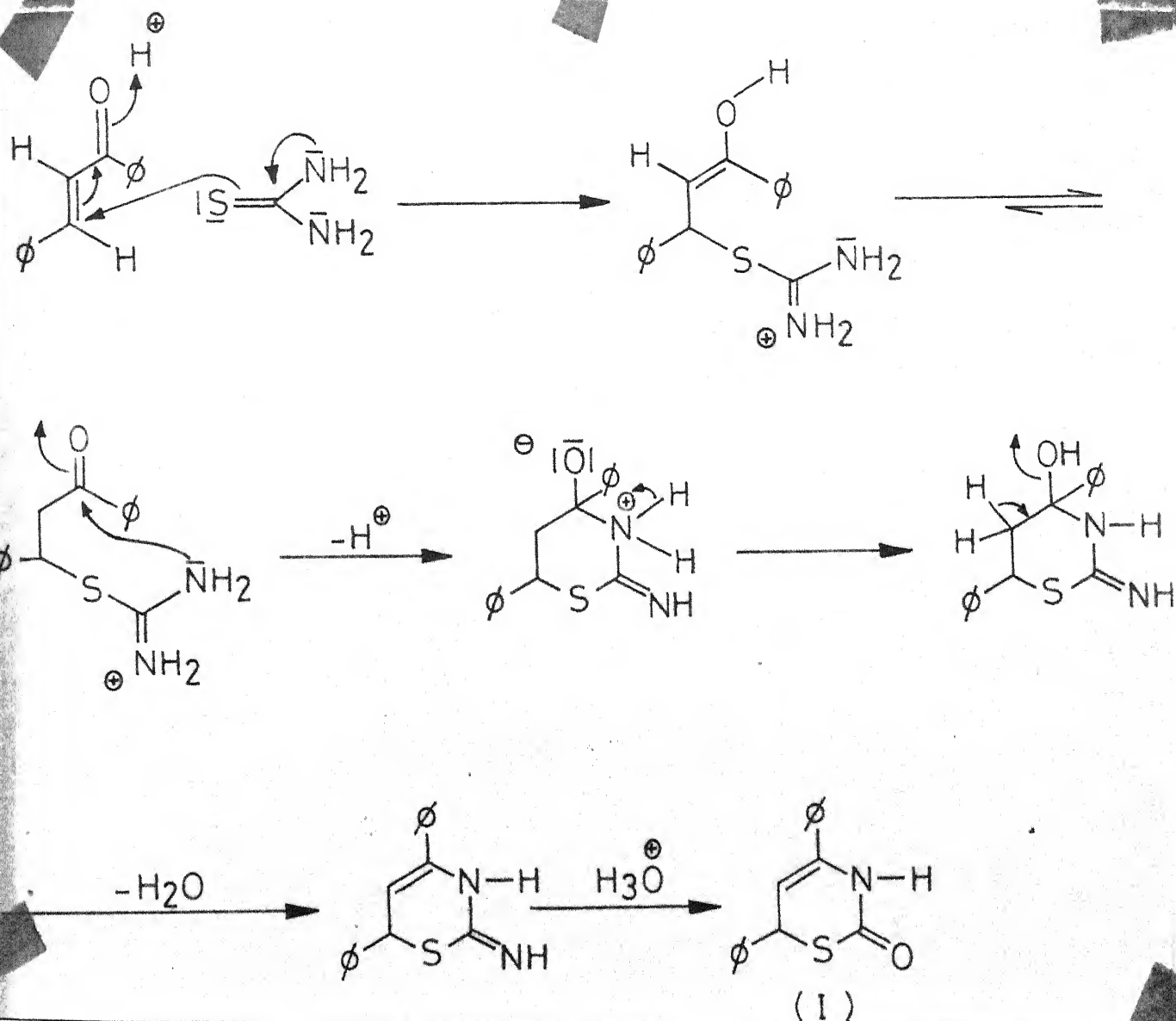
CHAPTER - 4.5

## REACTION OF CHALCONES WITH AMIDES

Urea.....	101
Thiourea.....	101
Cyanoacetamide.....	102
Malonamide.....	103
N,N-Dibromobenzenesulphonamide.....	103
Aromatic Thioamides.....	104
References.....	105

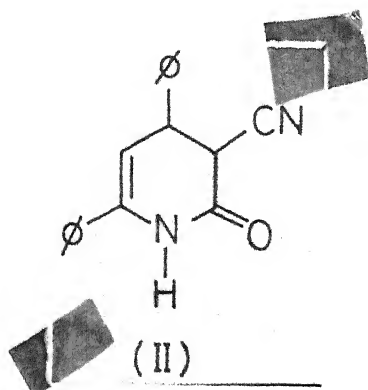
Urea: Chalcone reacts, under acid catalysis, with urea<sup>1</sup> to yield 2-oxo-4,6-diphenyl-1,2,3,4-tetrahydropyrimidine. Similar reaction is reported<sup>1</sup> to take place with arylidene bis ureas.

Thiourea: 2-oxo-4,6-diphenyl-3,6-dihydro-1,3-thiazine (I) is obtained<sup>2</sup> by the reaction of chalcone with thiourea, in the presence of dilute sulphuric acid. The formation of I has been rationalized<sup>2</sup> as follows:

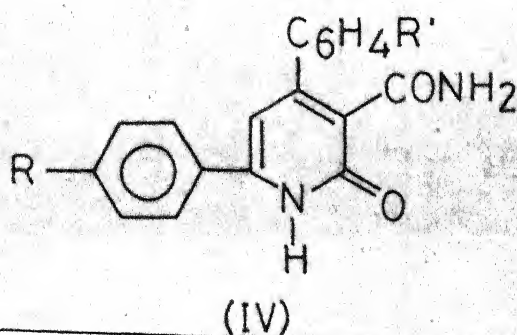
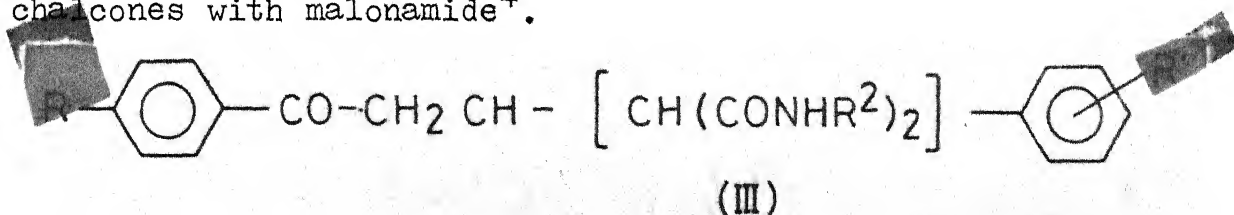


4-chloro-(and 4-methoxy) chalcones, however, yield their corresponding dimers<sup>2</sup>, when reacted under the above conditions.

Cyanoacetamide: Chalcone condenses with cyanoacetamide<sup>3</sup> to yield a nitrogen heterocycle (II)

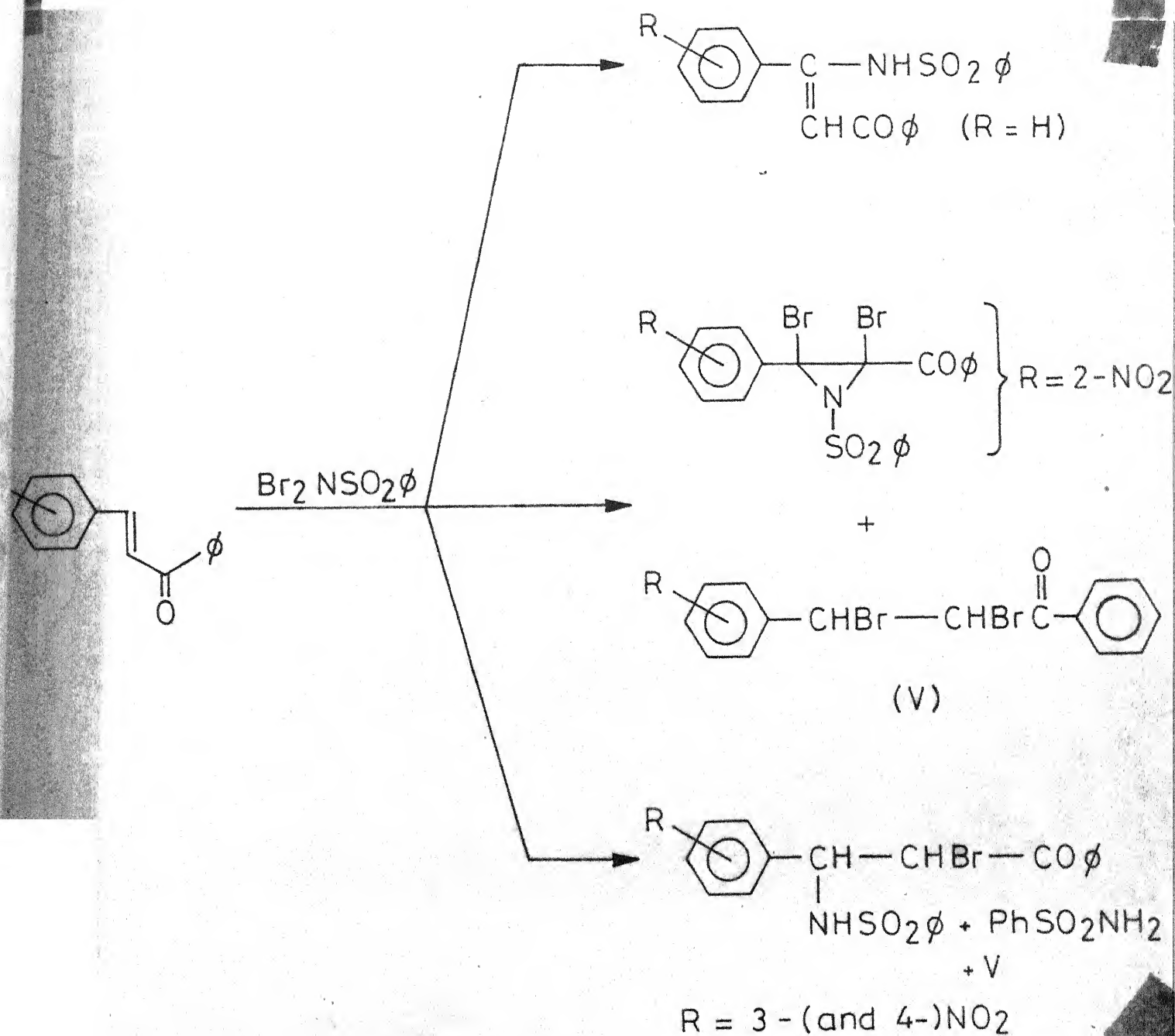


Malonamide: Depending upon the conditions of the experiment, different products (III or IV) are formed by the reaction of chalcones with malonamide<sup>4</sup>.



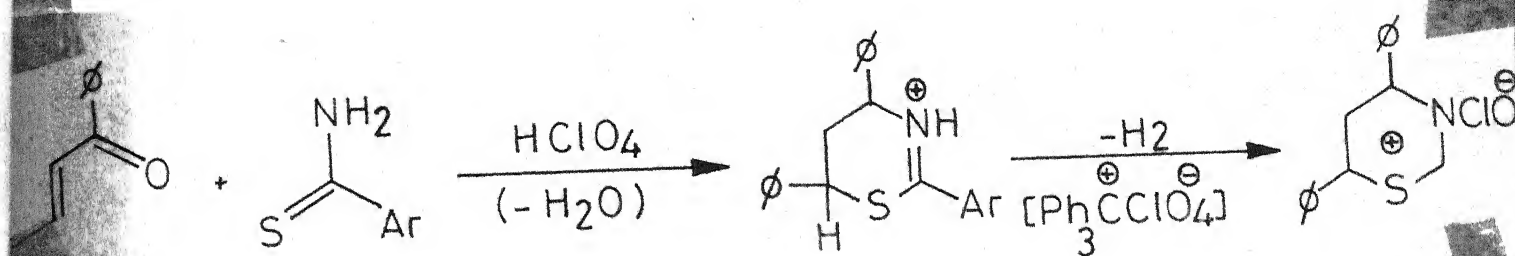
N,N-Dibromobenzenesulphonamide<sup>5,6</sup>:

The reaction of N,N-dibromobenzenesulphonamide with chalcones presents an interesting example. Thus different products<sup>6</sup> (vide infra) are formed with variously substituted chalcones:



### Aromatic Thioamides:

1,3-Thiazinium salts<sup>7</sup> derived from chalcone have been secured by the following series of reactions:



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CHAPTER - 4.6

## REACTION OF CHALCONES WITH CYANIDES, ISOCYANIDES AND ISOCYANATES

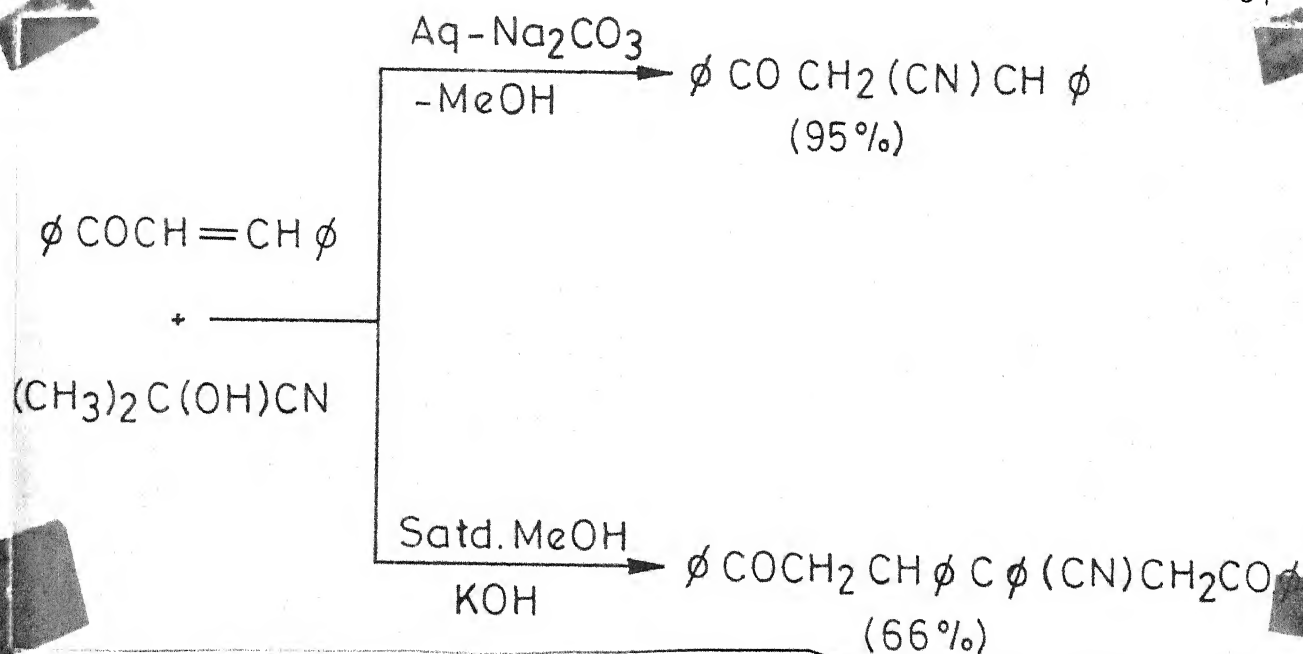
Hydrocyanic acid.....	106
Aliphatic and Alicyclic Nitriles.....	107
Benzonitrile and Acetonitrile.....	107
$\alpha$ -Dimethylaminophenylacetonitrile.....	108
Ethyl- $\gamma$ -Cyano- $\beta$ , $\gamma$ -Diphenylbutyrate.....	108
Potassium <del>I</del> cyanide.....	108
Chlorosulphonyl Isocyanate.....	109
References.....	110

Hydrocyanic acid:

Hydrocyanic acid is reported<sup>1</sup> to react with chalcone to yield an adduct,  $\text{OCH}(\text{CN})\text{CH}_2\text{COO}$ . The adduct has been transformed<sup>1</sup> into acid, lactone, pyridazinone, and diol under appropriate reaction conditions.

The exchange of hydrocyanic acid occurs between chalcone and acetone cyanohydrin<sup>2</sup> in the presence of a base. Reaction may take either of the following pathways-depending upon the condition of the experiment<sup>2</sup>. Thus:



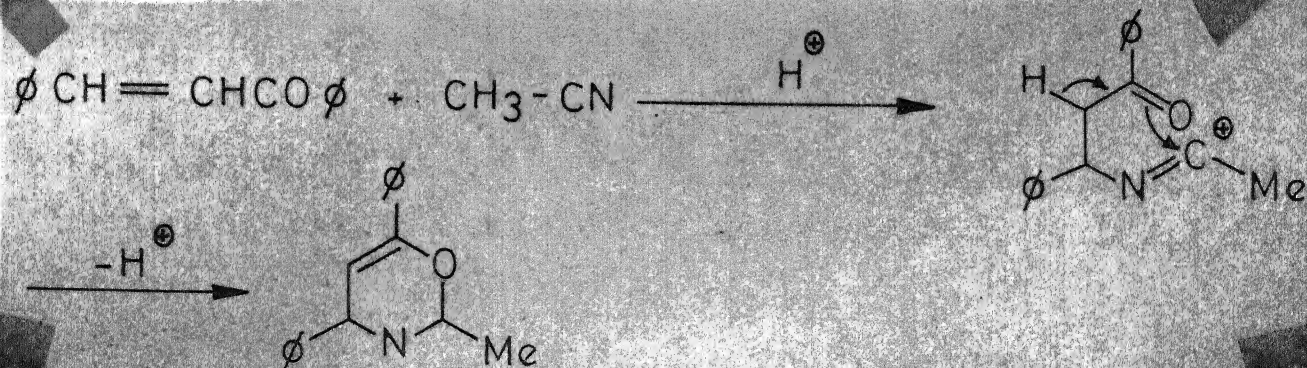


### Aliphatic and Alicyclic Nitriles:

Aliphatic nitriles,  $\text{RCH}_2\text{CN}$ , add across the carbonyl group of chalcone to give  $\beta$ -hydroxynitriles<sup>3</sup>. Thus, acetonitrile<sup>3</sup> reacts with chalcone in the presence of lithium amide in liquid ammonia, to give  $\phi\text{CH=CHC(OH)(CH}_2\text{CN)}\phi$ .

### Benzonitrile and Acetonitrile:

Chalcone behaves as a less satisfactory olefin component in the Ritter reaction. Thus benzonitrile reacted with chalcone in the presence of acid, resulting in the formation of 3-benzamido-3-phenylpropio-phenone<sup>4</sup> in a small yield. With acetonitrile, however, the end product is an oxazine<sup>4</sup>:



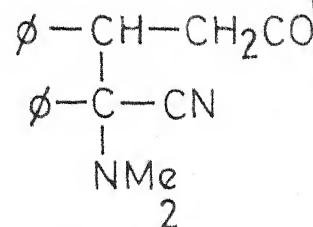
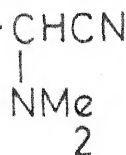
$\alpha$ -Dimethylaminophenyl Acetonitrile:

Chalcone undergoes conjugate addition with  $\alpha$ -dimethylaminophenyl acetonitrile, in the presence of potassium amide in liquid ammonia. The product  $\alpha, \beta, \delta$ -triphenyl- $\alpha$ -

i)  $\text{KNH}_2\text{-NH}_3(\text{l})$

ii)  $\phi\text{CH=CHCO}\phi$

iii)  $\text{NH}_4\text{Cl}$

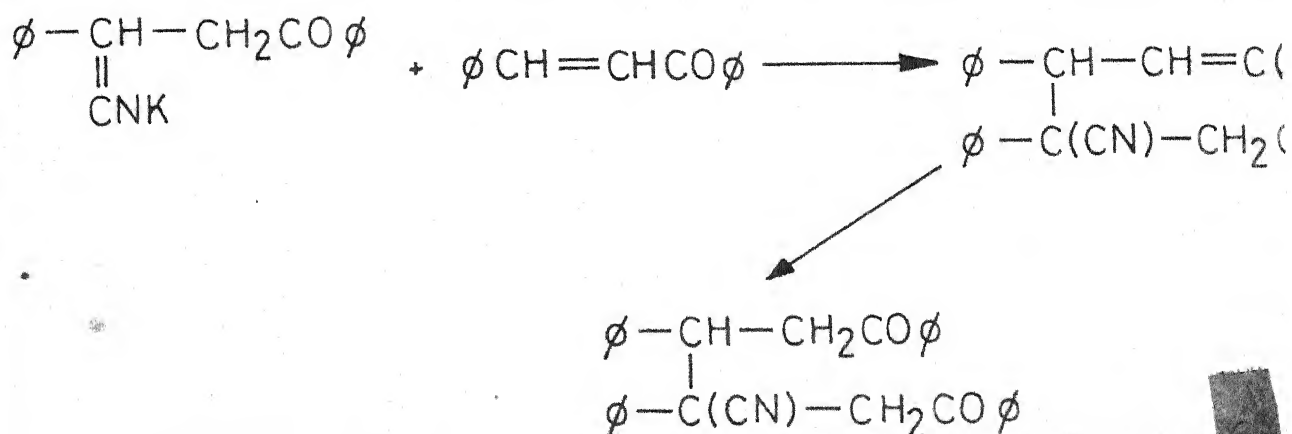
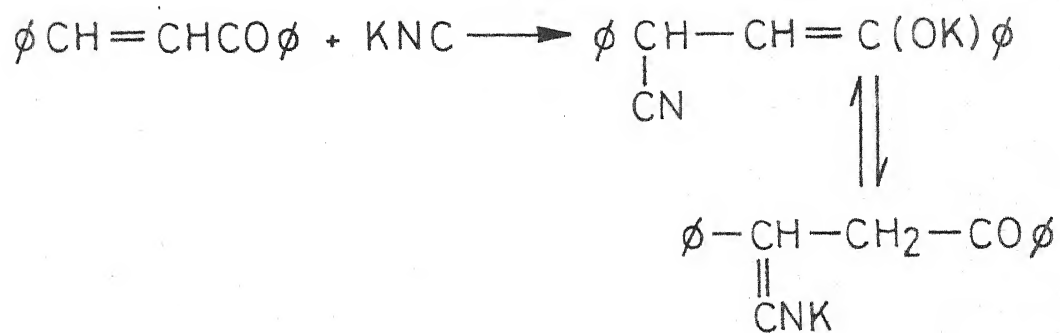


Ethyl- $\gamma$ -cyano- $\beta, \gamma$ -diphenylbutyrate:

Chalcone reacts with the title compound, in the presence of sodium ethoxide in ethanol, to give 3-benzoyl-4-keto-1,2,6-triphenylcyclohexanenitrile<sup>6</sup>.

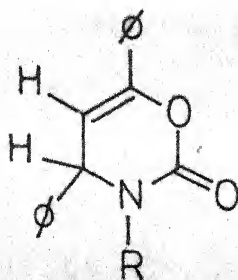
Potassium Isocyanide:

Chalcone and potassium isocyanide<sup>7</sup>, in boiling methanol, yield an addition product,  $\phi\text{CH} \left[ \text{C}\phi(\text{CN})\text{CH}_2\text{-CO}\phi \right] \text{CH}_2\text{CO}\phi$ , according to the following scheme:



#### Chlorosulphonyl Isocyanate:

Chlorosulphonyl isocyanate is reported<sup>8</sup> to react with chalcone to yield N-chlorosulphonyl-4,6-diphenyl-2-oxo-3,4-dihydro-1,3-oxazine (Ia, 55%); the latter compound on reduction



- (I) (a)  $\text{R} = \text{SO}_2\text{Cl}$   
 (b)  $\text{R} = \text{H}$

with thiophenol-pyridine gives I(b).

In the case of 4 (and 4')-methoxy chalcones, however, the reaction with chlorosulphonyl isocyanate leads to the formation of N-chlorosulphonylimine<sup>9</sup>,  $R'-C(=NSO_2Cl)CH=CH-R$ , via the unstable 1,3-oxazetidin-2-one.

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CHAPTER - 4.7

## REACTION OF CHALCONES WITH AMINES

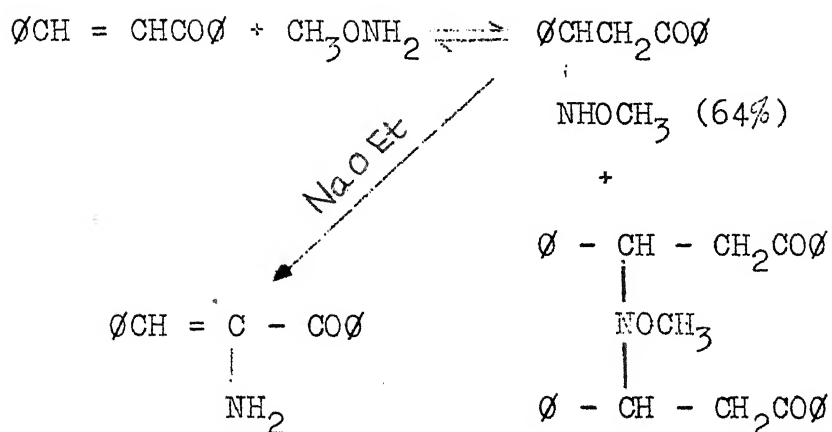
Methylamine.....	111
Methoxyamine.....	111
Aniline.....	112
1-Cyano-2-Methyl-2-aminoethylene.....	113
$\alpha$ -Aminobenzenethiol.....	113
Pyrrolidine.....	113
Iodine-amine Complexes.....	114
Triaminoguanidine Salt.....	116
Amidines.....	116
References.....	117

Methylamine:

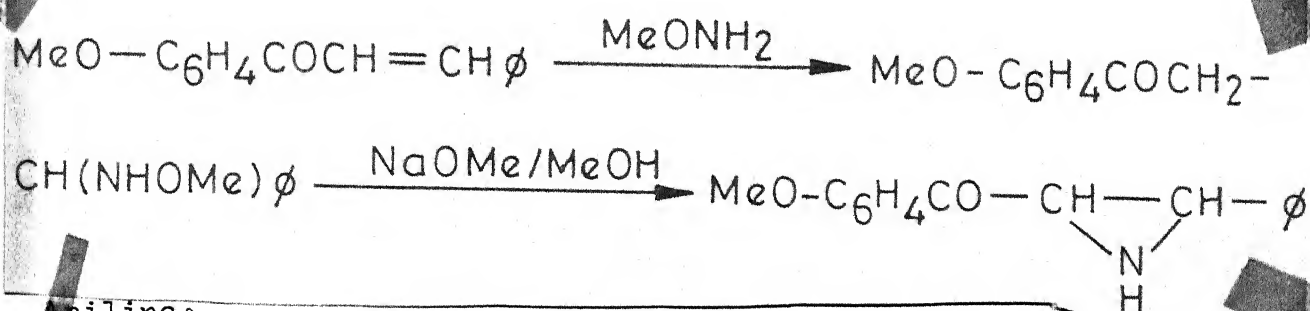
N,N-bis ( $\alpha$ -phenacylbenzyl) methylamine,  $[\text{CH}_3\text{N}(-\text{CH}\text{O})\text{CH}_2\text{CO}\text{O}]_2$  results by the interaction of chalcone with methylamine<sup>1</sup> in ethanolic solution.

Methoxyamine:

Methoxyamine<sup>2</sup> reacts with chalcone and its *p*- or *p'* substituted analogue to give the addition product,  $\beta$ -methoxyaminopropiophenone and  $\beta\beta'$ -methoxyimino-bis-propiophenone. In the presence of strong base, the addition product obtained, for example in the case of chalcone, undergoes rearrangement<sup>2</sup> to yield  $\alpha$ -aminochalcone (94%)



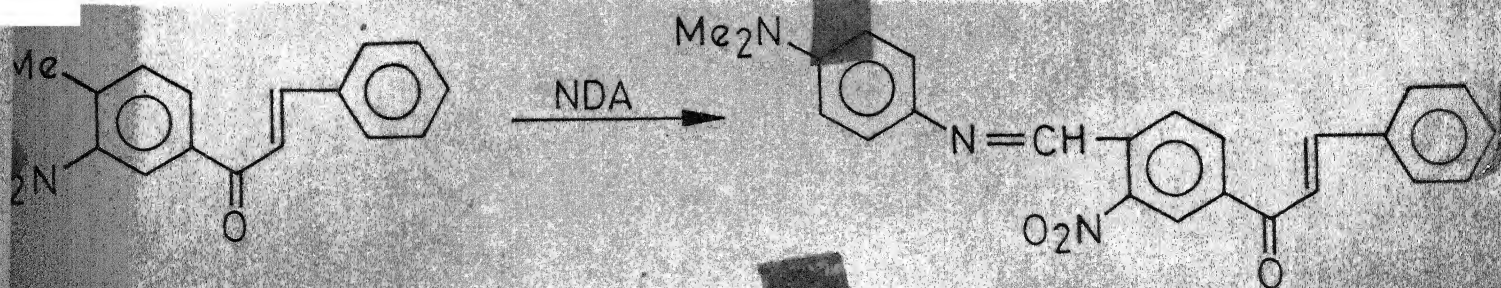
Aziridines have been prepared<sup>3</sup> from chalcones in the following way:



Aniline:

The addition product,  $\beta$ -anilino-benzylacetophenone<sup>4</sup>, is formed by the reaction of chalcone with aniline. In the case of other primary aromatic amines, the addition of the hydrochloride salt of the amine is preferred<sup>5</sup> and the yields of products range from 27-55%.

Nitromethylchalcones have been reported<sup>6</sup> to react with p-nitro-N,N-dimethylaniline (NDA), illustrating the reaction capacity of the methyl group.

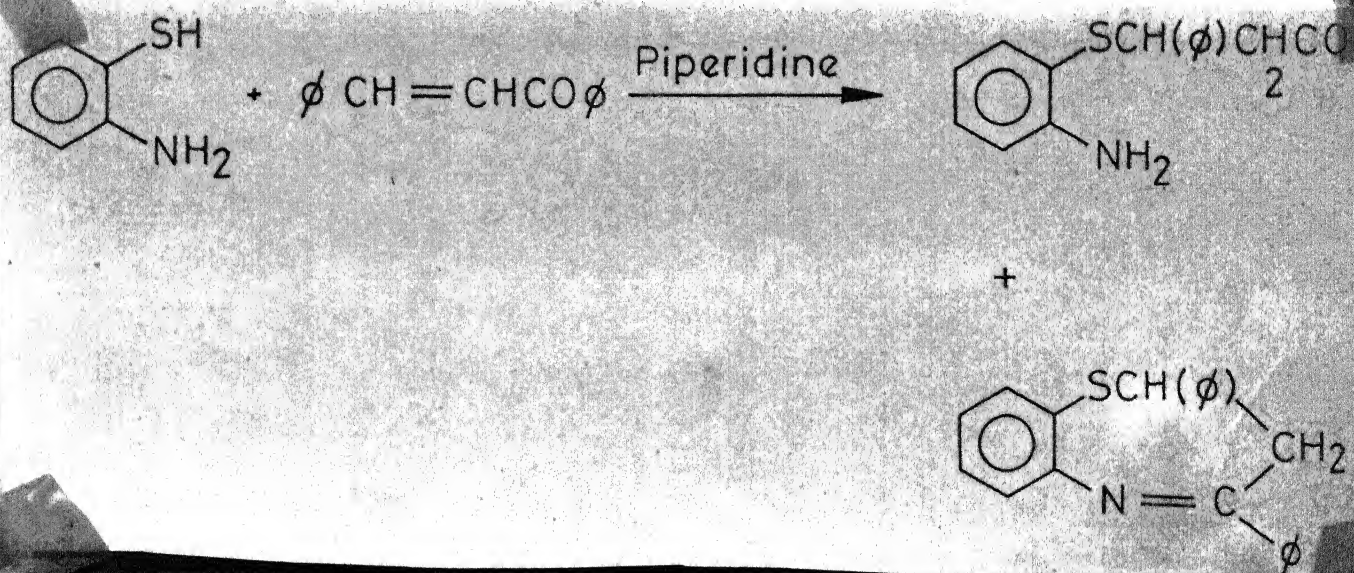


1-Cyano-2-Methyl-2-aminoethylene:

3-cyano-4-phenylpyridines have been secured by the reaction of 1-cyano-2-methyl-2-aminoethylene with chalcones, which have been subsequently transformed into 2-azafluorenones<sup>7</sup>.

$\alpha$ -Aminobenzenethiol:

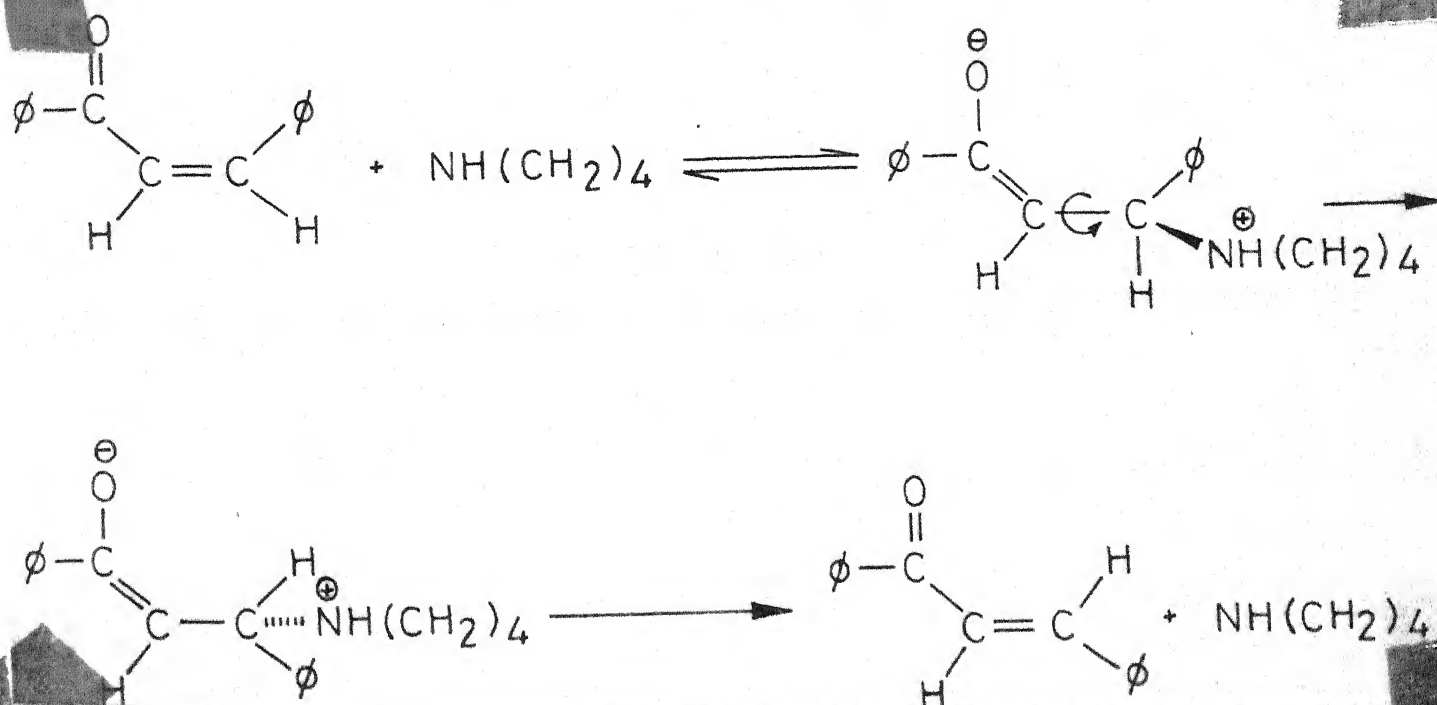
Two products are formed in the reaction of  $\alpha$ -aminobenzenethiol with chalcone, viz.,  $\beta$ -phenyl- $\beta$ -(*o*-aminophenylmercapto) propiophenone and its cyclised product: 2,4-diphenyl-6,7-benzo-1-thia-5-aza-4,6-cycloheptadiene<sup>8</sup>:



Pyrrolidine:

The reaction of cis- and trans-chalcones with pyrrolidine has been investigated<sup>9</sup>. It has been shown<sup>9</sup> that cis-chalcone changes to the corresponding trans-isomer (vide infra) before yielding the Michael adduct:



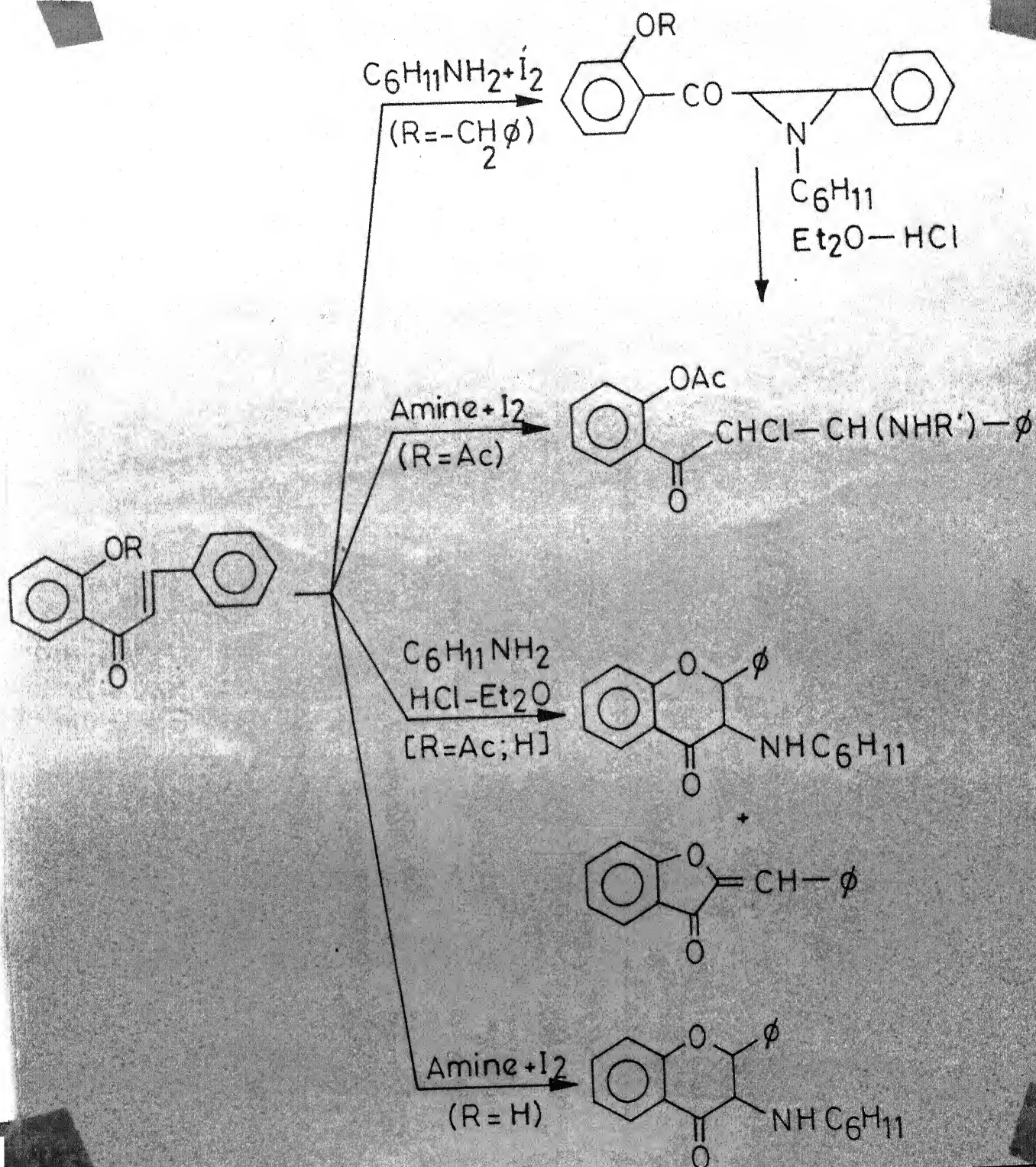


#### Iodine-amine Complexes:

Ethyleneimine ketones<sup>10</sup> are formed by the action of iodine complexes of ammonia or primary amines with chalcones.  $\alpha$ ,  $\beta$ -Diaminobenzylacetophenone, however, are produced when chalcone is reacted with a secondary amine-iodine complex.

It has been observed<sup>11</sup> that in the preparation of ethyleneimine ketone, the nature of solvent has a decisive influence upon the configuration of the end product. For example<sup>11</sup>, the reaction of trans-chalcone with cyclohexylamine iodine complex, in methanolic solution yields 88% of trans-1-cyclohexyl-2-phenyl-3-benzoyl-ethyleneimine as compared to 61-73% in benzene. On the other hand, substitution of methanol for benzene in reaction of cyclohexylamine with trans- $\alpha$ -bromochalcone greatly increased the proportion of cis-ethyleneimine ketone.

Ortho-substituted chalcone<sup>s</sup> react with amines,<sup>12,13</sup> in the presence of iodine, to give different products, depending upon the nature of the 2'-substituent. The following table illustrates the various products that are formed:



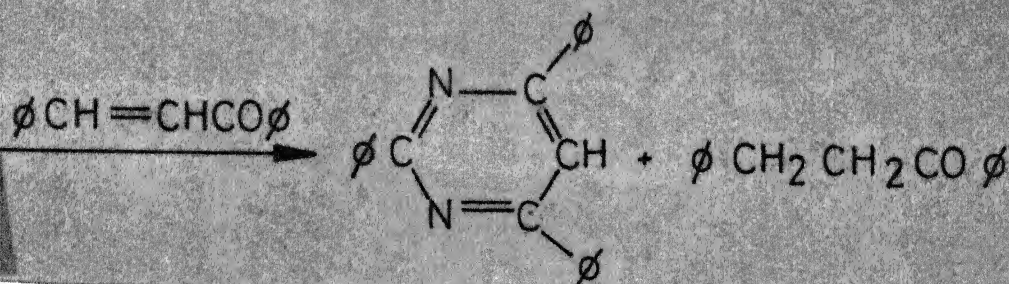
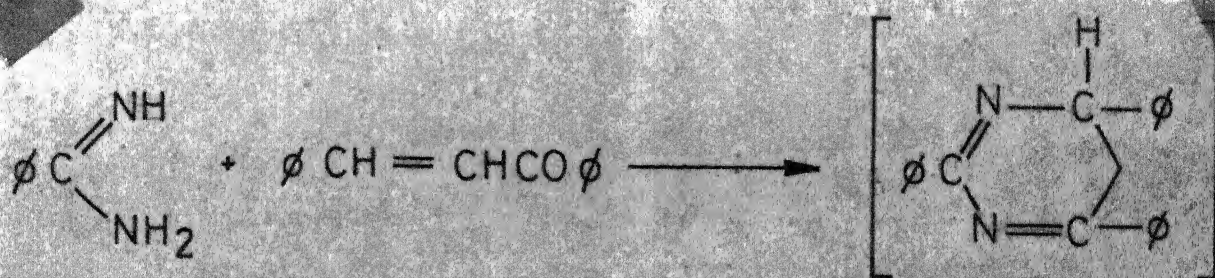
Triaminoguanidine Salt:

The reaction of chalcone with triaminoguanidine<sup>14</sup> is slow, and yields the corresponding hydrazone (75%) of the type:

$(RR'C = NNH)_2 C = N-N = CRR'$ , where R = Phenyl and R' = Styryl groups respectively.

Amidines<sup>15,16</sup>:

Amidine hydrochloride is reported to react with chalcone to yield the cyclo-addition product, viz., 2,4,6-triphenylpyrimidine, in 85% yield



In this reaction, a part of chalcone is reduced to the saturated ketone.

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CHAPTER - 4.8

## A. Reaction of Chalcones with Organometallic Compounds

Lithium Acetylide.....	120
Phenyl-alkali Metals.....	120
Benzhydryl Sodium.....	121
Aryl Copper.....	122
Diphenyl Beryllium.....	122
Diphenyl Mercury.....	122
Triphenyl Aluminium, Triphenyl Indium and Triphenyl Thallium.....	122
Triphenyl-methyl Sodium.....	122
Triphenyl-cadmium-lithium.....	123
Triphenyl-tin-lithium.....	123
Tetraphenyl Boro-copper.....	123

## B. Reaction with Organo-magnesium Compounds

Methyl Magnesium Bromide.....	123
Ethyl Magnesium Bromide.....	123
<u>n</u> -Butyl Magnesium Bromide.....	124
Phenyl Magnesium Bromide.....	124
Organo-Magnesium Compounds.....	125
Amino-Magnesium Compounds.....	125
References.....	126

### A. Reaction with Organometallic Compounds

#### Lithium Acetylide:

The reaction of chalcone with lithium acetylide in liquid ammonia yields the corresponding ethynyl carbinol<sup>1</sup> (1:2-adduct) in a good yield (81%).

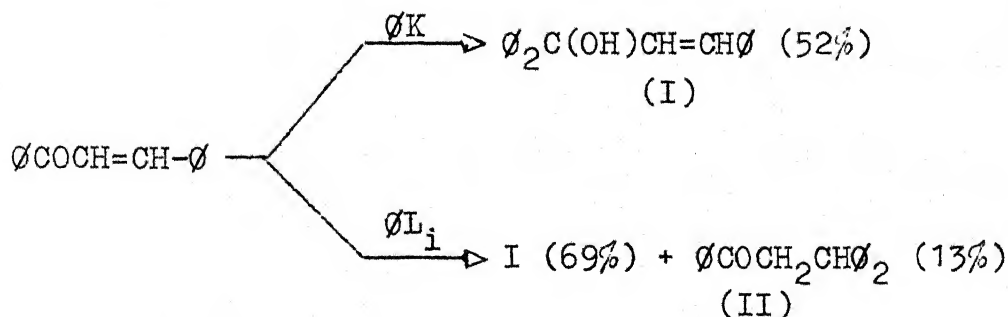
#### Phenyl-alkali Metals:

Phenyl lithium, phenyl sodium and phenyl potassium react with chalcone to yield mainly the 1,2-addition products<sup>2</sup> (60-75%):



(M = Li, Na or K)

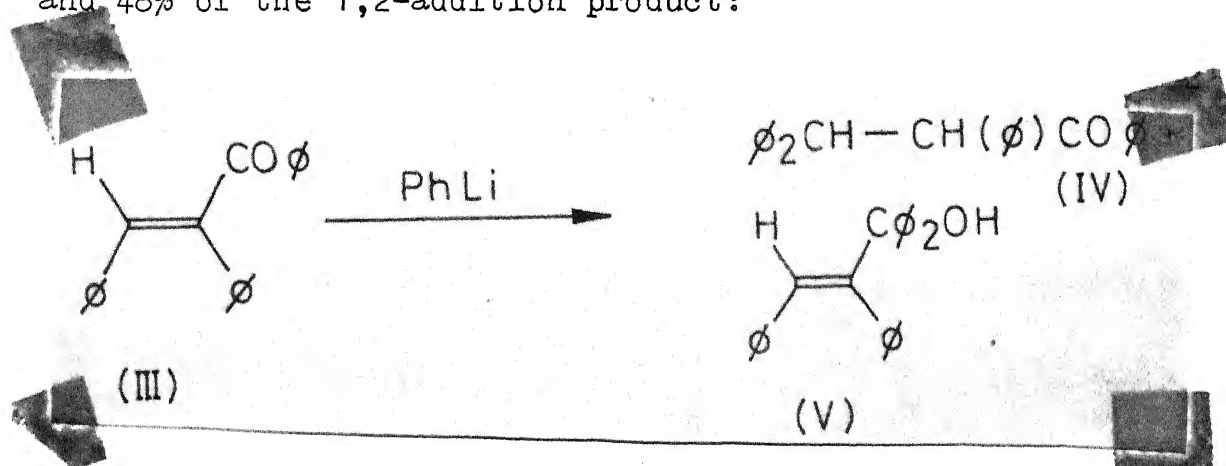
The mode of addition of the organometallic compound to chalcone depends upon the reactivity<sup>3</sup> of the former. In these cases, the addition may occur either across the double bond and/or the carbonyl group of chalcone molecule. The following examples are illustrative:





Reaction with excess phenyl lithium is reported<sup>4</sup> to yield 1,1,2,3,3-pentaphenyl propanol besides the diphenyl styryl carbinol (I).

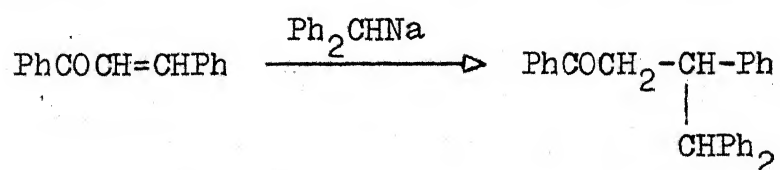
Phenyl lithium is also reported<sup>5</sup> to add to trans- $\alpha$ -phenylchalcone (III), yielding 33% of the 1,4-addition product (IV) and 48% of the 1,2-addition product:



Low temperature reaction of chalcone with phenyl lithium, followed by decomposition of the reaction-mixture with water gives two products<sup>6</sup>, viz.,  $\text{PhCH}=\text{CHCPh}_2\text{CH}$  (84%) and  $\text{Ph}_2\text{CH}=\text{CH}_2\text{COPh}$  (16%) respectively.

#### Benzhydryl Sodium:

Chalcone reacts with benzhydryl sodium<sup>7</sup> according to the following reaction:



Aryl Copper:

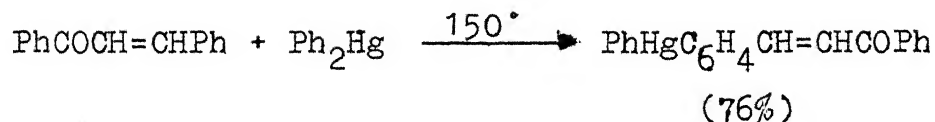
Chalcone reacts with aryl copper<sup>8</sup> in the presence of aryl iodide, under Ullmann conditions, to give among other products,  $\beta$ -aryl chalcone in small amounts.

Diphenyl Beryllium:

Diphenyl beryllium<sup>3</sup> reacts with chalcone to give  $\text{PhCOCH}_2\text{CHPh}_2$  in a high yield ( $\sim 90\%$ ).

Diphenyl Mercury:

Diphenyl mercury<sup>9</sup> reacts with chalcone in the manner indicated:

Triphenyl Aluminium, Triphenyl Indium and Triphenyl Thallium:

$\beta\beta'$ -Diphenylpropiophenone is obtained when chalcone is reacted with triphenyl aluminium<sup>10</sup> or triphenyl indium.<sup>11</sup> Under the same reaction conditions, triphenyl thallium,<sup>12</sup> however, yields an additional product, viz.,  $\beta'$ -phenyl- $\gamma$ -benzhydryl-butyrophenone (30%).

Triphenyl Methyl Sodium:

The title reagent is reported<sup>4</sup> to react with chalcone to yield 2,3,3,3-tetraphenylpropyl phenyl ketone (25-35%).

Triphenyl-cadmium-lithium:

Chalcone and triphenyl-cadmium-lithium<sup>13</sup> react to give, after hydrolysis, three products, viz., diphenylpropiophenone (21%), diphenyl styryl carbinol (6%) and  $\beta$ -phenyl- $\gamma$ -benzoyl- $\gamma$ -benzhydrylbutyrophenone (1.8%).

Triphenyl-tin-lithium:

Tetraphenyl-tin<sup>14</sup> (7.8%) is produced in the reaction of chalcone with triphenyl tin lithium.

Tetraphenyl boro-copper:

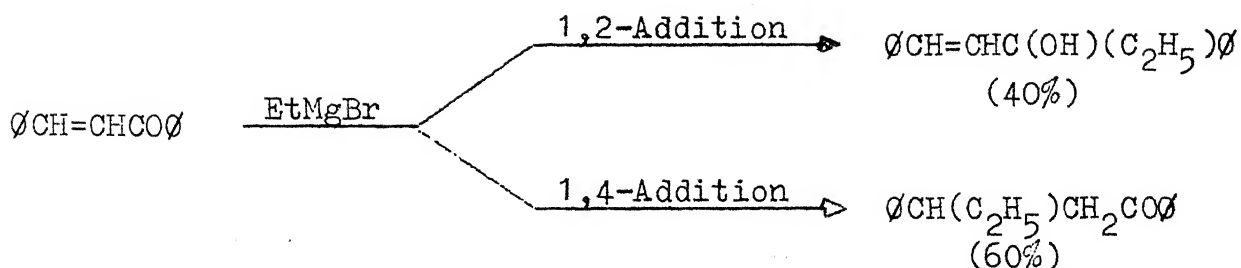
The pyridine salt of tetraphenyl boro-copper<sup>15</sup> and chalcone after reaction furnish  $\beta\beta$ -diphenylpropiophenone (29%).

B. Reaction With Organo-magnesium CompoundsMethyl Magnesium Bromide:

Chalcone reacts with excess of methyl magnesium bromide to yield the 1,4-addition product,  $\beta$ -phenyl-butyrophenone<sup>16,17</sup> or the bimolecular compound.<sup>17</sup> Sometimes a secondary product, viz., 1,3,5-triphenyl-4-benzoylhex-1,3-diene is obtained.

Ethyl Magnesium Bromide:

The products formed in the reaction of chalcone with ethyl magnesium bromide corresponds to 1,2- and 1,4-addition.



The effect of some metallic chlorides on the reaction of chalcone with Grignard reagents is reported.<sup>16</sup> For the formation of reduction dimers, cobalt chloride acts as a powerful catalyst compared to cuprous and ferric chlorides.

#### n-Butyl Magnesium Bromide:

The relative activities of chalcones, carrying an  $\alpha$ - or  $\beta$ -methyl substituents towards n-butyl magnesium bromide have been studied.<sup>18</sup>  $\beta$ -Methyl compounds are reported<sup>18</sup> to be more reactive in comparison to their  $\alpha$ -isomers.

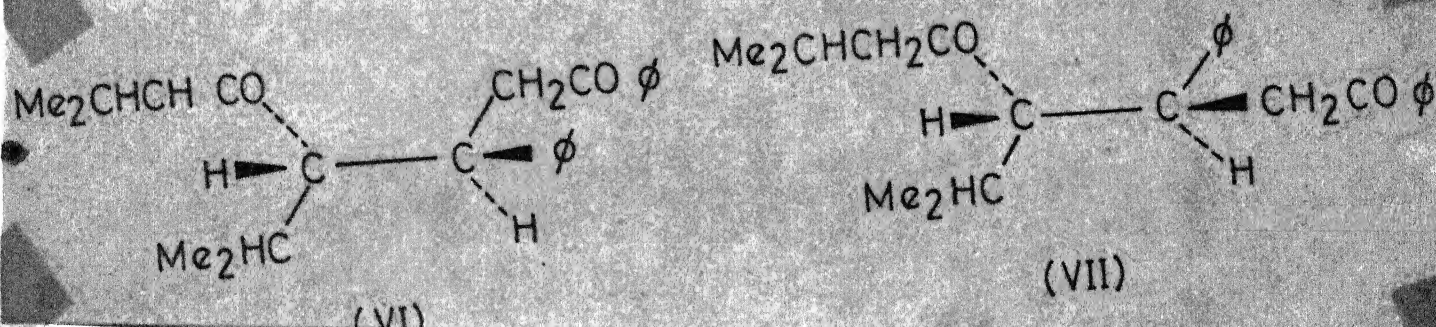
#### Phenyl Magnesium Bromide:

The reaction of the trans chalcone with two equivalent of phenyl magnesium bromide yields two products, viz., 3,3-diphenylpropiophenone<sup>19,20</sup> (83%) and trans-1,1,3-triphenyl-2-propen-1-ol (6%) respectively. However, a different product,<sup>21</sup> viz., 1,1,3,3-tetraphenyl-1-propanol results by varying the experimental conditions in the above reaction. Variation in the manner of work-up of the Grignard reaction mixture, namely the treatment with dry ice, is reported<sup>21,22</sup> to yield 2-benzhydryl-3-hydroxy-3,3-diphenylpropionic acid.

The mode of addition of phenyl magnesium bromide to chalcone depends upon the chemical nature of the substituents.<sup>23</sup> Thus, the principal product of the reaction with 4-carboethoxychalcone is a saturated ketone, while in the case of 4-dimethylaminochalcone, the product is an  $\alpha, \beta$ -unsaturated alcohol.<sup>23</sup>

#### Organo-magnesium Compounds:

The Grignard reaction of trans chalcone with  $\text{Me}_2\text{CHCH}_2\text{COCHXCHMe}$  ( $\text{X} = \text{Cl}, \text{Br}$ ) and  $[\text{Me}_2\text{CHCH}_2\text{COCH}(\text{CHMe}_2)]_2\text{Mg}$  is reported<sup>24</sup> to give two diastereoisomeric diketones (VI and VII)



The reaction of various magnesium carbonyls with trans-chalcone has been studied.<sup>25</sup> Whether the addition occurs at carbonyl or olefinic sites of chalcone, depends upon the nature of the added nucleophile.

#### Amino-magnesium Compounds:

Dynopinacols (50-70%) have been secured<sup>26</sup> by the interaction of chalcones with dynones under the influence of an amino-magnesium compound.

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CHAPTER - 4.9REACTION OF CHALCONES WITH HALOGENS, PSEUDO-HALOGENS AND  
INTER-HALOGEN COMPOUNDS

Chlorine.....	128
Bromine.....	128
Kinetics of Bromine Addition.....	129
Debromination of Chalcone Dibromides.....	129
Iodine Monochloride.....	130
Bromine Fluoride and Bromine Chloride.....	130
Chlorine Thiocyanate, Thiocyanogen and Iodine Thiocyanate..	131
References.....	131

Chlorine:

Chalcone reacts with chlorine to yield two stereoisomeric chalcone  $\alpha$ ,  $\beta$  dichlorides.<sup>1</sup> The dichlorides<sup>2,3</sup>, under appropriate reaction conditions are convertible to  $\alpha$ -chlorochalcone (80%).

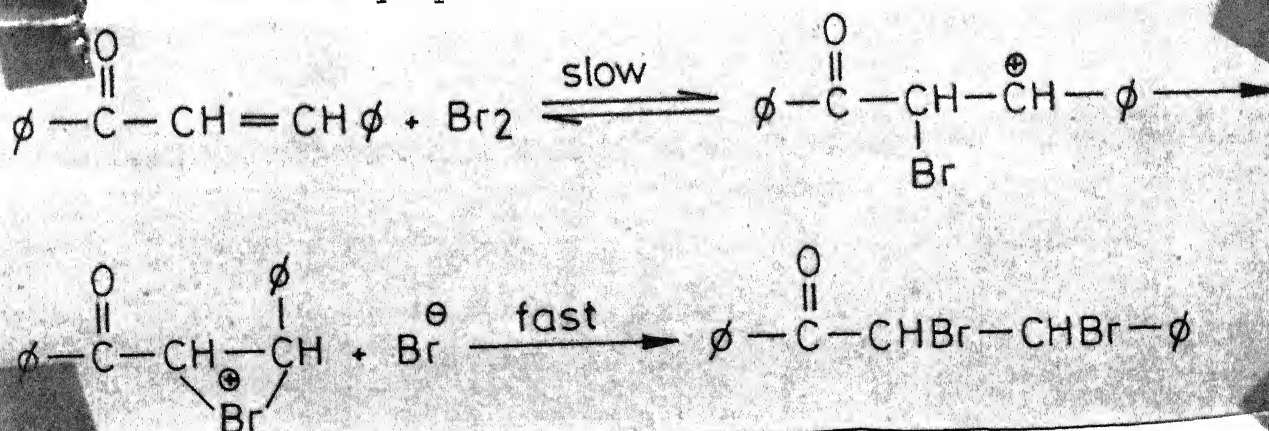
Bromine:

A large number of chalcone  $\alpha$ ,  $\beta$  dibromides have been prepared.<sup>3-13</sup> Bromination is effected either by the reaction of bromine<sup>3-9,11-13</sup> (in carbon disulphide or acetic acid), tetrabromo-o-benzoquinone<sup>10</sup> 1-bromo-2-methyl-2-imidazoline hydrobromide<sup>14</sup> or 1,3-dibromo-5,5'-dimethylhydantoin<sup>15</sup> on

chalcones. The reaction with bromine is sometimes attended with nuclear bromination<sup>11-13</sup> (ring A and/or ring B of chalcone) depending upon the reaction conditions employed.

#### Kinetics of Bromine Addition:

The kinetics of bromine addition to chalcone and its derivatives have been investigated<sup>16,17</sup> and a two-step mechanism of this reaction has been proposed<sup>18</sup>:

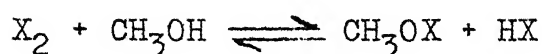


#### Debromination of Chalcone Dibromides:

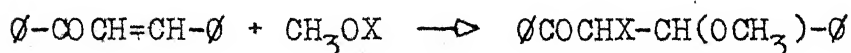
Chalcone  $\alpha$ ,  $\beta$  dibromides on treatment with potassium iodide in acetone are reported<sup>3,7</sup> to undergo debromination to yield the respective chalcones. Debromination has been achieved<sup>19</sup> by reacting the chalcone dibromide with stannous chloride in various solvents, viz., acetone, tetrahydrofuran and dimethylformamide.

In a methanolic solution, chalcone reacts with bromine (at 25-30°) to give a mixture of two products,<sup>20,21</sup> viz.,  $\alpha$ -bromo- $\beta$ -methoxy- $\beta$ -phenylpropiophenone (23%) and chalcone  $\alpha$ ,  $\beta$ -dibromide (5%). The yield of the former product is raised if the reaction is conducted at higher temperature (65°). Likewise  $\alpha$ -chloro- $\beta$ -

methoxy- $\beta$ -phenylpropiophenone<sup>21</sup> has been secured in 56% yield by conducting the reaction of chalcone with chlorine (in methanol) at 25-30°. The mechanism of the reaction has been postulated<sup>21</sup> as follows:



(X = Cl, Br)

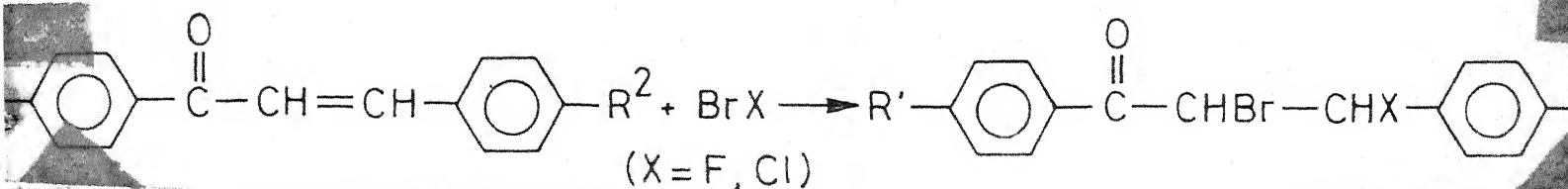


#### Iodine Monochloride:

Treatment of chiral crystals of 4,4'-dimethylchalcone with chlorine, bromine or iodine monochloride is reported<sup>22</sup> to yield optically active dihalides. The reaction of iodine chloride and 2'-hydroxychalcone has been shown<sup>23</sup> to yield products depending upon the nature of substituent(s). Thus iodine chloride reacts with 2'-hydroxy-3',5'-dimethyl-4-methoxychalcone to yield 3-iodo-6,8-dimethylflavanone. Chalcone lacking in strong electron donor substituent (e.g., methoxy), however, undergoes addition reaction with iodine chloride. Nevertheless, nuclear halogenation, in preference to addition reaction, is reported to occur in one case, viz., 2'-hydroxy-4',6'-dimethoxychalcone.

#### Bromine Fluoride and Bromine Chloride:

Bromine fluoride<sup>24</sup> and bromine chloride<sup>25</sup> are reported to add to the olefinic double bond of chalcone molecule, thus:



Chlorine Thiocyanate, Thiocyanogen and Iodine Thiocyanate:

Chlorine thiocyanate, thiocyanogen and iodine thiocyanate<sup>26</sup> add across the double bond of chalcone molecule. From the addition products, obtained in the first two cases,  $\alpha$ -thiocyanatochalcones have been secured by dehydrohalogenation.

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CHAPTER - 5

## CYCLISATION REACTIONS OF SUBSTITUTED CHALCONES

Formation of Flavanones.....	134
$\alpha$ - or $\beta$ -Cyclisation.....	135
Formation of Benzylidene-Coumaranones, Chromones and	
Chromanones.....	136
Flavonols, Aurones and Dihydroflavonols.....	136
Flavones.....	139
Isoflavones.....	141
Cyclisation of 2'-hydroxy-2-nitrochalcone.....	142
References.....	143

Formation of Flavanones:

The conversion of substituted 2'-hydroxychalcones into their corresponding flavanones is usually effected under the influence of mineral acids.<sup>1-16</sup> The optimum time of reaction, in the presence of phosphoric acid, has been reported<sup>8</sup> to be in the range of 20-30 hours. The reaction time, however, varies with the nature of alcohol used as a solvent.<sup>8</sup> Higher alcohols are not suitable since these promote side reactions. The yield of flavanones is, by and large, independent of the concentration of phosphoric acid.<sup>8</sup>



The preparation of  $\underline{d}$ -7-hydroxyflavanone has been achieved<sup>1</sup> by heating 2',4'-dihydroxychalcone with  $\underline{d}$ -camphorsulphonic acid. The temperature and duration of heating are reported<sup>1</sup> to be important factors for the production of maximum optical activity.

Some of the hydroxynitro chalcones (bearing a 2'-hydroxyl) have been cyclised to their corresponding flavanones. The chelation of the nitro group with 2'-hydroxyl is an important parameter in determining the stability of chalcone in respect of its conversion to flavanone.<sup>7</sup>

Oftentimes dilute alkali has been used<sup>17,18</sup> to bring about the cyclisation of polyhydroxychalcones (taking butein as an example) into their corresponding flavanones. The synthesis of several flavanones and 3-benzylidene flavanones, using appropriately substituted chalcones as the starting materials, are reported in the literature.<sup>19-32,37,38</sup>

The quantitative influence of substituent effects on the cyclisation kinetics of 2'-hydroxychalcone into flavanone has been studied.<sup>33</sup> Reaction mechanisms have been proposed<sup>34-36</sup> for this type of transformation.

#### $\alpha$ - or $\beta$ -Cyclisation<sup>39</sup>:

The  $\alpha$ - or  $\beta$ -cyclisation of chalcone to yield aurone or flavanone depends upon the nature of the  $\alpha$ -substituent (with respect to the carbonyl group) and pH of the reaction medium.

Amongst the parameters regulating the  $\beta$ -cyclisation ~~include~~ include the stability of the resulting flavanones, acidity of the 3-protons and the presence of a 5-hydroxylic function.

#### Formation of Benzylidene Coumaranones, Chromones and Chromanones:

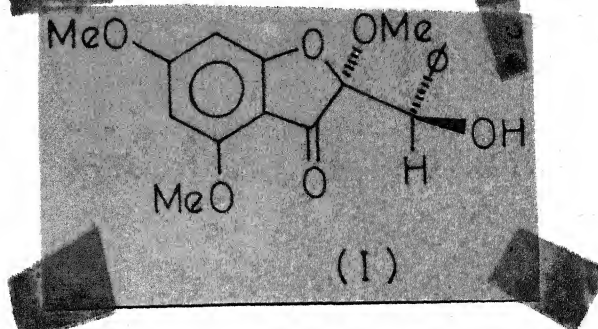
Under appropriate reaction conditions hydroxychalcones have been transformed into benzylidene-coumaranones<sup>40-42</sup> and hydroxychromones.<sup>43,44</sup>

By carrying out the AFO reaction on 2'-hydroxychalcones, containing an  $\alpha$ -phenyl substituent, the synthesis of chromanones has been achieved.<sup>45</sup>

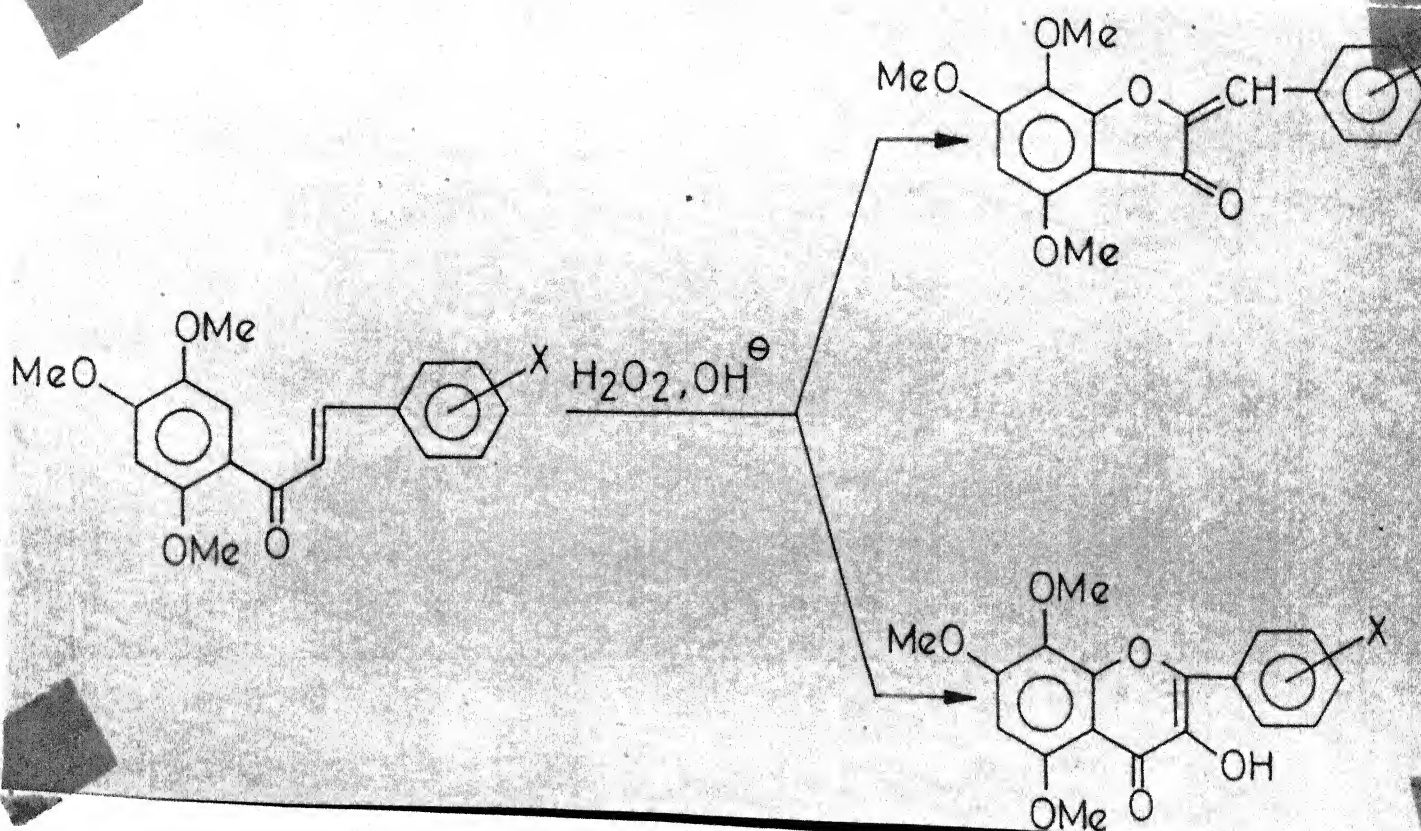
#### Formation of Flavonols<sup>11,12,25,26,40-42,46-51,67,70,89,90</sup>

#### Aurones and Dihydroflavonols<sup>64</sup>:

2'-Hydroxychalcones on oxidation with alkaline hydrogen peroxide give flavonols.<sup>11-13,40-42,46-54</sup> This reaction is often referred to as Algar-Flynn-Oyamada (AFO) reaction. However, if there is a methoxy<sup>55</sup> or methyl substituent at 6'-position in chalcone,<sup>55-57</sup> aurones are formed, provided there is no hydroxylic function present at 2- or 4-positions<sup>58,59</sup> and that the reaction is carried out at room temperature. An aurone derivative (I) isolated in the AFO reaction of 2'-hydroxy- $\alpha$ ,4',6'-trimethoxychalcone has been shown<sup>60</sup> to have an erythro configuration.

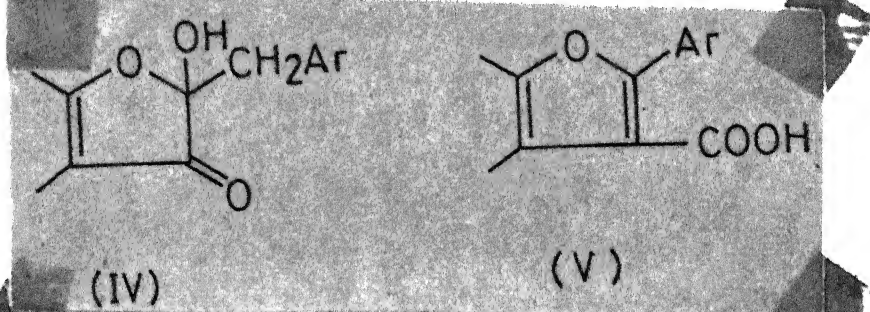


In some cases, however, mixture of aurone and flavonol are obtained.<sup>61</sup> For example:



Similar results have been reported<sup>62</sup> in respect of 2',4'-dihydroxy-3'-nitrochalcone (II) and 2',6'-dihydroxy-3'-nitrochalcone (III) when these are treated with pyridine and alkaline hydrogen peroxide. Thus, under these reaction conditions, II yield 7-hydroxy-8-nitroflavonol<sup>62</sup> and III gives the corresponding aurone.<sup>62</sup> The chalcone bearing a nitro substituent ( $X=\text{NO}_2$ ) however, fails to undergo the AFO reaction.<sup>61</sup>

Two additional products (IV and V) are reported<sup>63,64</sup> to be formed in the AFO reaction of chalcone. The rationale for the formation of these compounds is described.<sup>65</sup>

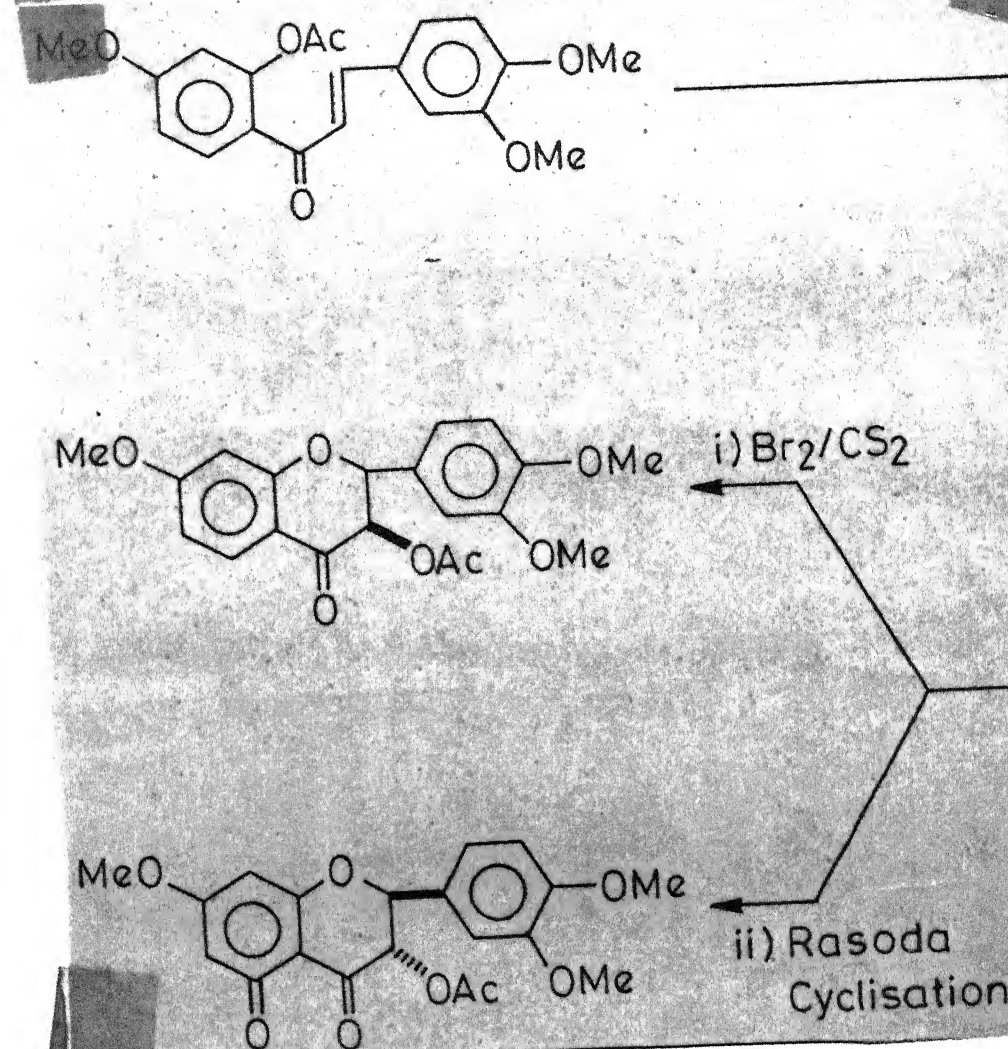


A detailed mechanism of AFO reaction has been published.<sup>66</sup>

Flavanones<sup>24,25</sup> can also be converted into flavonols, with alkaline hydrogen peroxide. In this case the reaction is reported<sup>24-25</sup> to proceed through the intermediacy of 2'-hydroxychalcone and dihydroflavonol.

Hydroxyflavonols<sup>67</sup> have been secured by the rearrangement of  $\alpha$ -nitrochalcone epoxides.

The geometric isomers of dihydroxyflavonols have been prepared.<sup>68</sup> The following sequence of steps were employed, for example, in the synthesis of cis and trans-3',4';7-trimethoxydihydroflavonols.



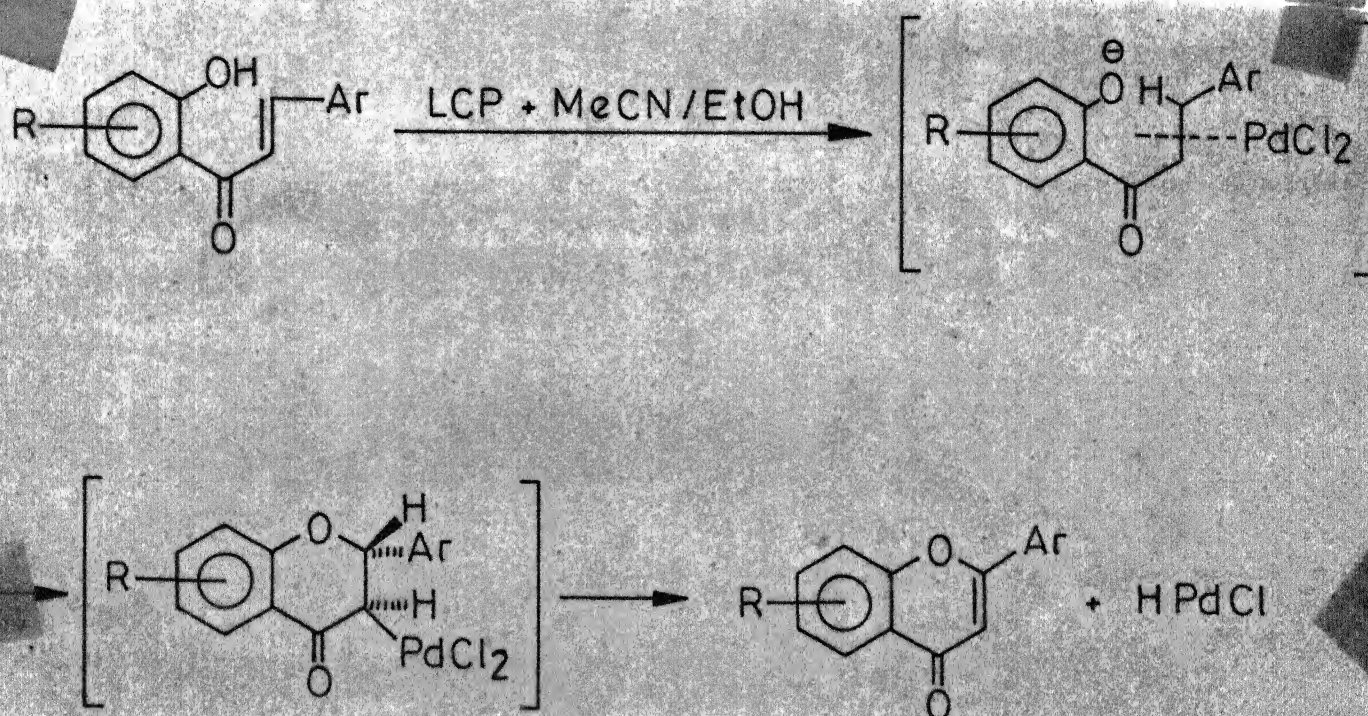
### Formation of Flavones:

Flavones have been prepared from appropriately substituted chalcones either by their oxidation with selenium dioxide,<sup>13,23,31,69-81</sup> or by heating with palladium black.<sup>82,83</sup> Cirsimaritin – a flavone derivative, for example, has been secured<sup>71</sup> by the reaction of 2'-hydroxy-4-benzoyloxy-4',5',6'-trimethoxychalcone with selenium dioxide, followed by debenzoylation and partial demethylation. The syntheses of naturally occurring flavones,<sup>74</sup> viz., cirsiliol and cirsilineol are based



on the aforesaid reaction. 7-Hydroxyflavone, on the other hand, has been secured<sup>82</sup> in 35% yield by heating (at 220°) 2',4'-dihydroxychalcone with palladium.

An alternative method<sup>84</sup> of preparing flavones in high yield, consists in the reaction of 2'-hydroxychalcone (sodium salt) with lithium chloropalladite (LCP). The following mechanism has been postulated for the reaction.

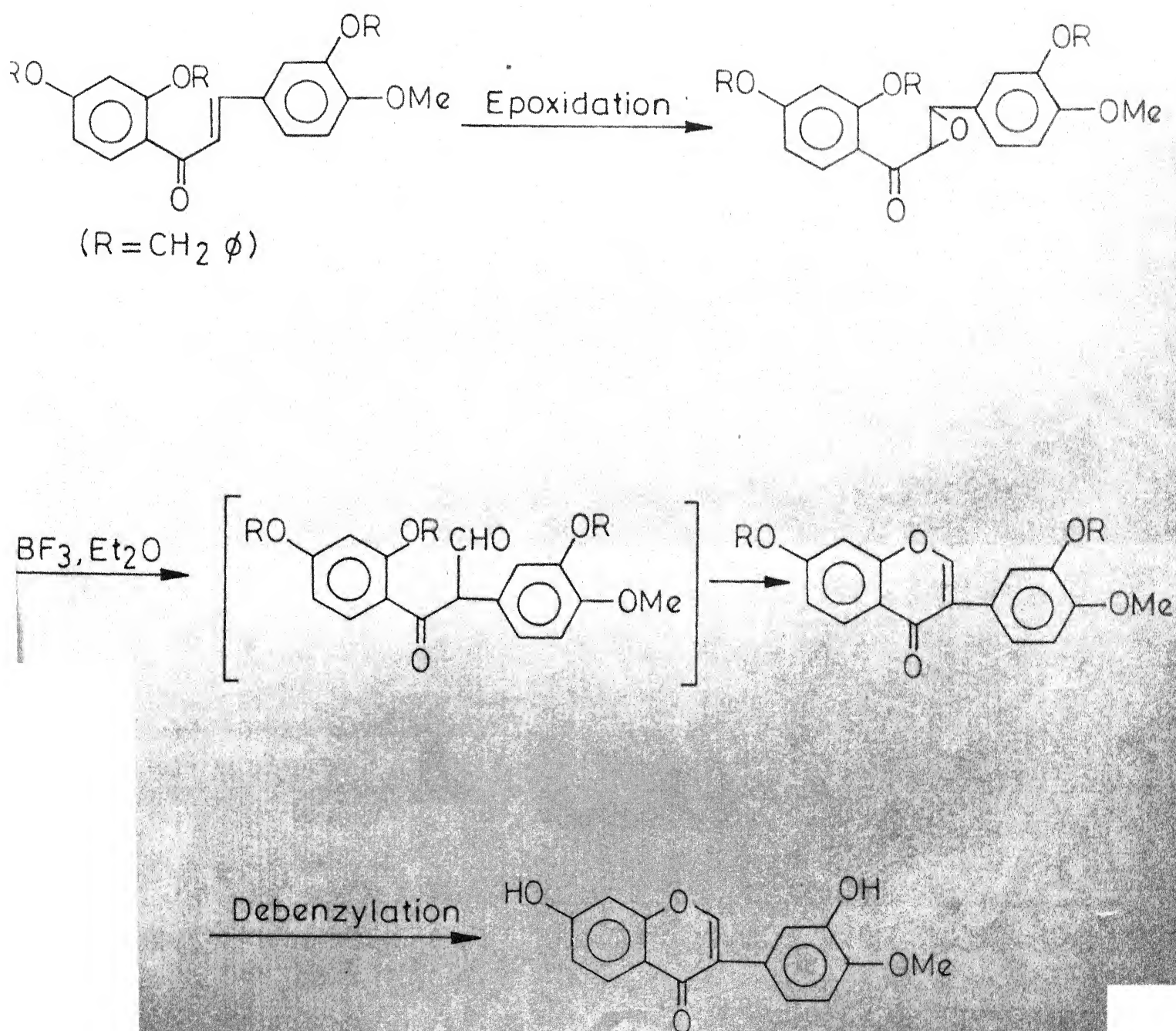


obtained as a mixture of axial and equatorial isomers, from 2'-hydroxy-4-methoxychalcones by initial bromination, followed by iodine catalysed cyclisation of the resulting chalcone dibromide.

Formation of Isoflavones:

Two approaches<sup>85-87</sup> have been made for effecting the synthesis of isoflavones and are illustrated by the following two examples:

3',7-Dihydroxy-4'-methoxyisoflavone has been prepared<sup>85</sup> by the following series of reactions:





Formation of Isoflavones:

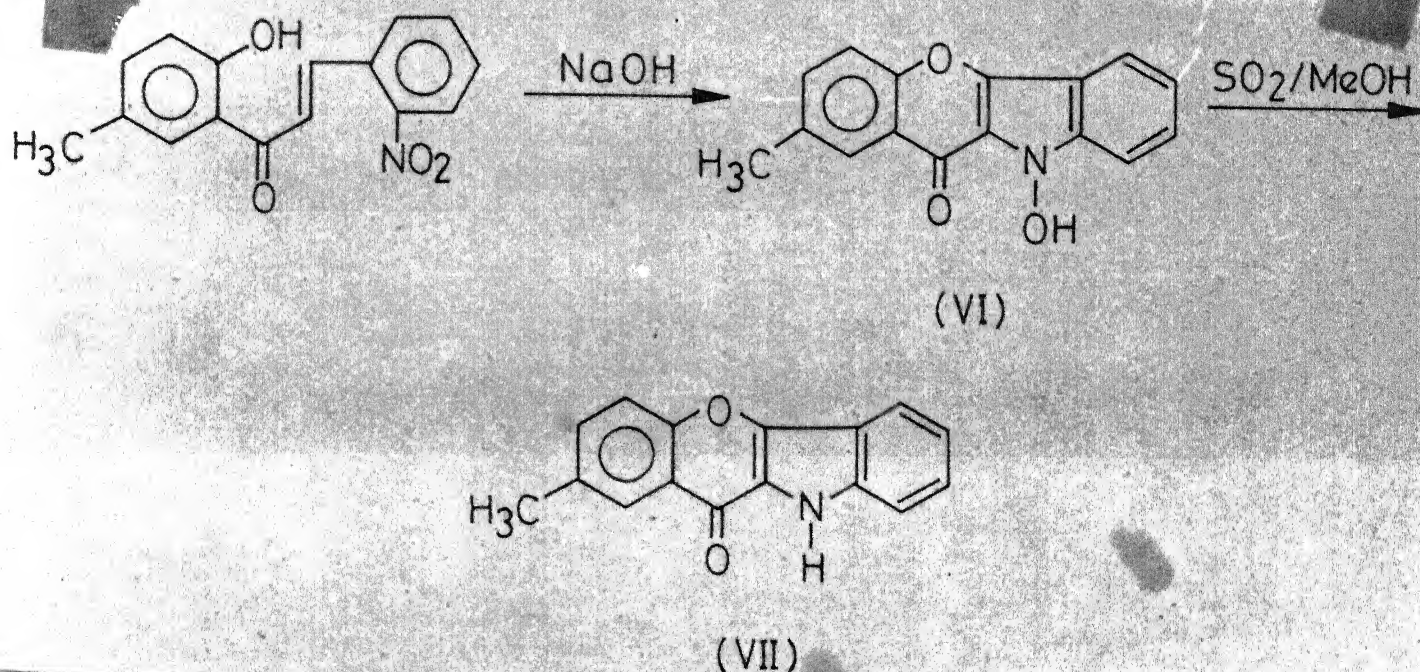
Two approaches<sup>85-87</sup> have been made for effecting the synthesis of isoflavones and are illustrated by the following two examples:

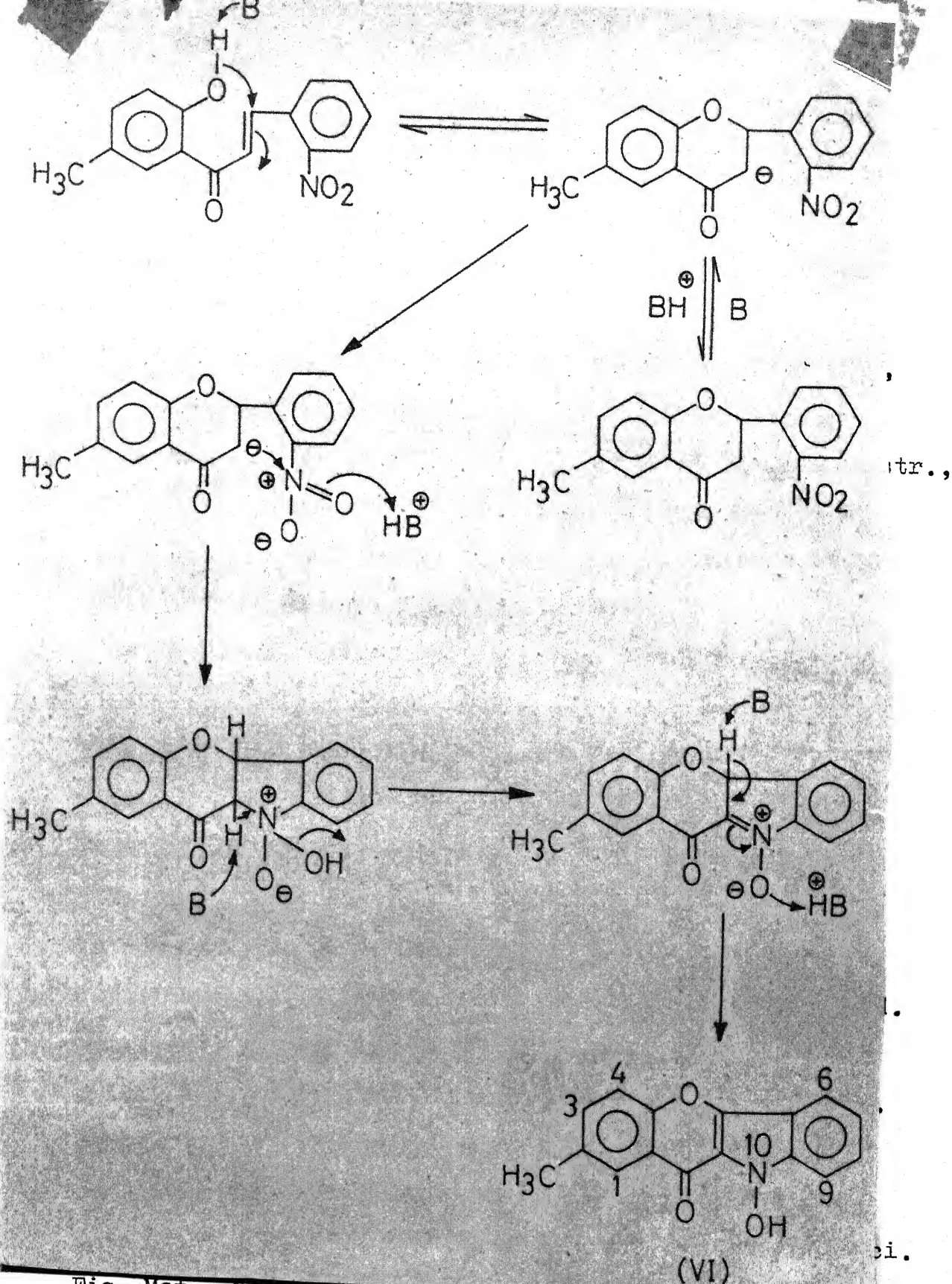
3',7-Dihydroxy-4'-methoxyisoflavone has been prepared<sup>85</sup> by the following series of reactions:

The naturally occurring 2',3',4',6,7-pentamethoxy- and 2',4',5',6,7-pentamethoxy isoflavones have been secured<sup>86</sup> by the action of thallic nitrate on appropriately substituted chalcones.

Cyclisation of 2'-hydroxy-2-nitro-5'-methyl chalcone<sup>88</sup>:

The title compound undergoes cyclisation in the presence of caustic alkali, to yield 10-hydroxy-2-methyl-11H[1]-benzopyrane [3,2-b]-indole 11-one, (VI). Treatment of the latter with sulphur dioxide in methanol yields the following compound (VII):





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## CHAPTER - 6

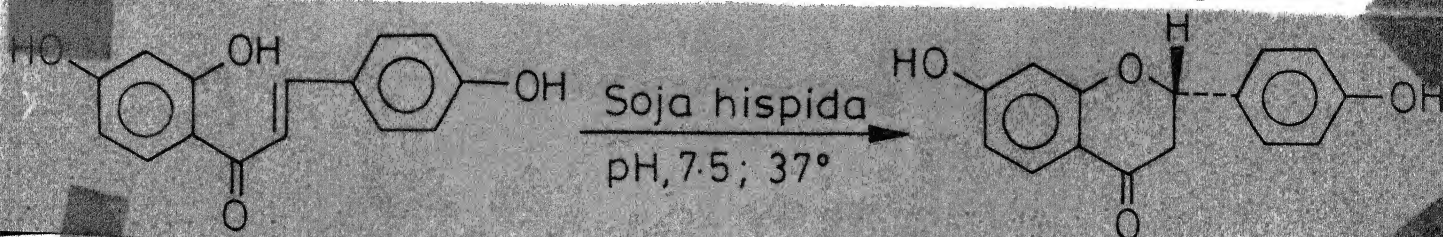
### BIOCHEMICAL CYCLISATION AND DEGRADATION OF CHALCONES

Formation of Flavanones.....	151
Benzalcoumaranone.....	152
Flavonol and Aurone.....	152
Anthocyanin and Other Flavonoids.....	153
Degradation of Chalcones.....	153
References.....	154

#### Formation of Flavanones:

The inter-conversion of chalcone and flavanone, with phloroglucinol type of substitution, has been accomplished<sup>1</sup> at pH = 7, by the aid of enzyme isolated from the peel of Citrus aurantium. Other sources of the enzyme are the peels of C. natsudaia, C. junos, C. nobilis, C. pseudoparadisi and Poncirus trifoliata.

2',4,4'-Trihydroxychalcone has been successfully isomerized<sup>2</sup> to the optically active 4',7-dihydroxy-flavanone, by the mediation of the isomerase isolated from soyabean seedling:



However, the chalcone-flavanone isomerase isolated either from the young leaves of Datisca cannabina<sup>3</sup> or from three different seedlings,<sup>4</sup> viz., phaseolus aureus, Cicer arietinum and Petroselinum hortense has failed in its action on chalcone glucoside, including those having a resorcinol type<sup>3</sup> of substitution in ring A. It is interesting to note that the chalcone isomerase isolated either from the flowers of Apeldoorn tulips or Lilium candidum<sup>5</sup> is active against 2',4,4',6'-tetrahydroxy-chalcone, but is ineffective against 2',4,4'-trihydroxychalcone.

Several studies have been reported<sup>6-9</sup> about the chalcone-flavanone isomerase activity in plants. The chalcone-flavanone isomerase obtained from soyabean seeds has been purified.<sup>10</sup> The kinetics of the isomerisation reaction, viz., isoliquiritigenin to liquiritigenin, conducted under the influence of the aforesaid enzyme has been examined.<sup>10</sup>

#### Formation of Benzal-coumaranone:

Enzyme catalysed transformation, at pH 5-6, of hydroxy-chalcone glycoside to hydroxy benzalcoumaranone glycoside has been reported.<sup>11</sup> The required enzyme is obtained by alcoholic extraction of the macerated rays of Coreopsis lanceolata.

#### Formation of Flavonol and Aurone:

Under aerobic conditions and in the presence of trace quantity of hydrogen peroxide, isoliquiritigenin (2',4,4'-

trihydroxychalcone) undergoes catalyzed oxidation by Horse-raddish peroxidase<sup>12</sup> to yield 4',7-dihydroxyflavonol and 4',6-dihydroxyaurone. A similar reaction occurs under the influence of cell-free extracts of hypocotys obtained from Phaseolus vulgaris.

#### Formation of Anthocyanin and Other Flavonoids:

It has been established that 2',3,4,4',6'-penta-hydroxychalcone-4'-glucoside serves as a precursor in the synthesis of anthocyanin<sup>13,14</sup> and other flavonoids<sup>15</sup> in Petunia hybrida.

On the basis of radioactive labelled feeding experiments it has been shown<sup>16,17</sup> that chalcones, rather than flavanones, are the intermediate precursors in the synthesis of other flavanoids. 2',4,4'-Trihydroxychalcone is reported<sup>18</sup> to be a precursor in the biosynthesis of coumestrol in the seedlings of Phaseolus aureus. Further, it has been shown<sup>19</sup> that there is maximum incorporation of the aforesaid chalcone into amorphenin by germinating Amorpha frutucosa seeds.

#### Degradation of Chalcones:

A few cases of degradation by chalcones brought about by plant cell suspension cultures have been reported.<sup>20,21</sup> For example, 2',4,4',6'-tetrahydroxychalcone-2'- $\beta$ -D-glucoside<sup>21</sup> undergoes degradation by callus suspension cultures of Pisum

sativum L., into para-hydroxybenzoic acid and 3-(hydroxyphenyl)-prop-2-enoic acid.

The chalcone content in the peel of pine apple fruit is reported<sup>22</sup> to decrease with maturity.

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CHAPTER - 7

## MISCELLANEOUS REACTIONS OF CHALCONES

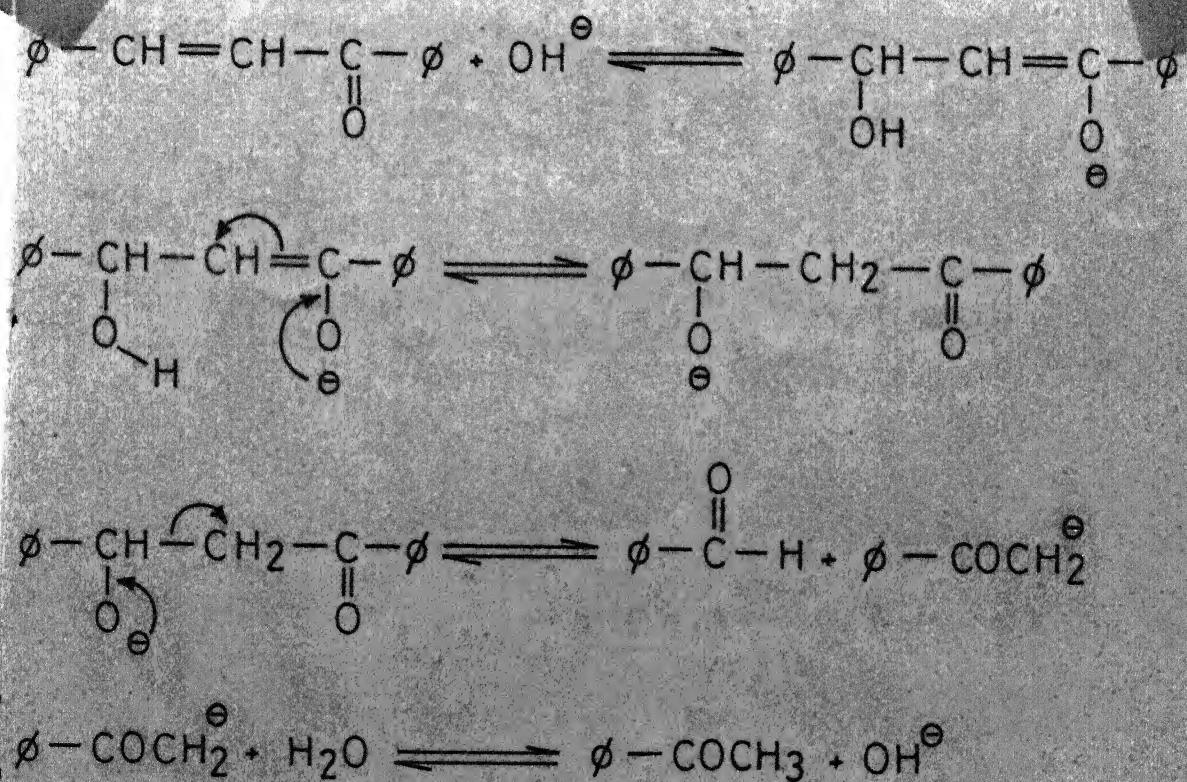
With Caustic Alkali.....	158
Sulphuric Acid.....	159
Polyphosphoric Acid.....	160
Phenylacetic Acid.....	160
Sodium Bisulphite.....	160
Alkali Sulphide.....	161
Anhydrous Aluminum Chloride.....	161
Nitrosoyl Chloride.....	163
Sodium Amide.....	163
Mercury Salts.....	163
Iron Carbonyls.....	164
Tritium.....	165
Heavy Water.....	165
Deuterioethanol.....	165
Benzene and Nitroparaffins.....	165
Diazomethane.....	166
1,1-Diethylaminoprop-1-yne.....	166
Alcohols.....	167
Thiols.....	168
Selenols.....	168
3,5-Dimethoxyphenol.....	169
2-Aminothiophenol.....	169

Ketenes.....	169
Benzoyl Chloride.....	171
Benzyl- <i>p</i> -tolylsulphone.....	171
Sulfenyl Compounds.....	172
Dimethyl Sulphonium and Sulphoxonium Methylides.....	172
Betaine Like Methylene Triphenylphosphorane.....	173
Nitrone.....	173
Nitrogen Heterocycles.....	174
Hydrazoic Acid.....	174
Hydroxylamine.....	176
Hydrazine.....	176
Phenylhydrazine.....	177
2,4-Dinitrophenylhydrazine.....	178
Hydrazine Derivatives.....	178
Disubstituted Phosphine Oxide.....	179
N-Bromosuccinimide.....	179
Bromine Azide.....	180
Pyrolysis.....	180
Autocondensation.....	181
Copolymerization of Chalcones/Analogues of Chalcone with	
Styrene.....	181
Butadiene.....	182
Acrylonitrile.....	182
Isoprene.....	182

Synthesis of <u>m</u> -polyphenyls.....	182
1,3-Diphenylglycerol.....	184
Aryl Benzyl Ethanolamines.....	184
References.....	184

### With Caustic Alkali<sup>1</sup>:

The olefinic bond in the chalcone molecule undergoes cleavage when refluxed with concentrated alkali (i.e., 0.3 molar)<sup>2</sup> giving rise to acetophenone and benzaldehyde. Kinetic study<sup>3</sup> of the above reaction has been carried out, and mechanism<sup>2,4</sup> have<sup>5</sup> been put forward to explain the formation of these products:



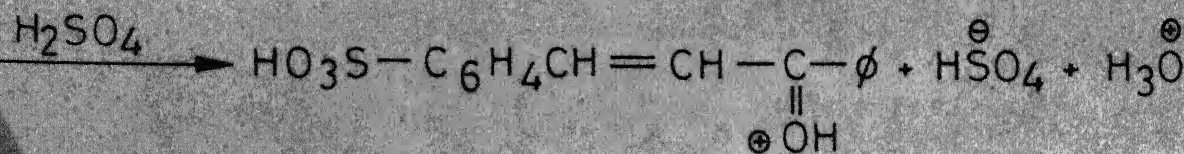
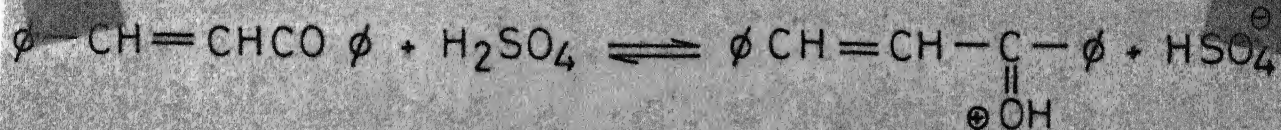
hydroxide ions.<sup>3,5</sup>

In case of some chalcones, higher molecular weight compounds have been isolated.<sup>6</sup> Thus anisal-bis(3,4-dimethoxy-acetophenone)<sup>6</sup> is produced by the reaction of caustic alkali with 3',4,4'-trimethoxychalcone.

With Sulphuric Acid:

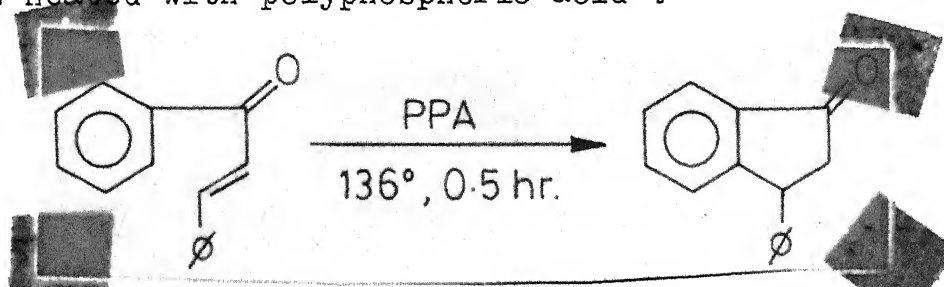
Chalcones usually show halochromic effects when wetted with concentrated sulphuric acid (vide halochromism). Some chalcones remain unchanged on this treatment, while others are susceptible to sulphonation,<sup>7</sup> in ring B. Thus 4-methoxy chalcone and 4,4'-dimethoxychalcone are converted, in the above reaction, to their corresponding sulphonic acid derivatives, while 4'-methoxychalcone remains unaffected.

The following reactions take<sup>7</sup> place when chalcone is reacted with sulphuric acid. The first step is the protonation of the carbonyl oxygen followed by the slow formation of monosulphonic acid<sup>8</sup>:



With Polyphosphoric Acid (PPA):

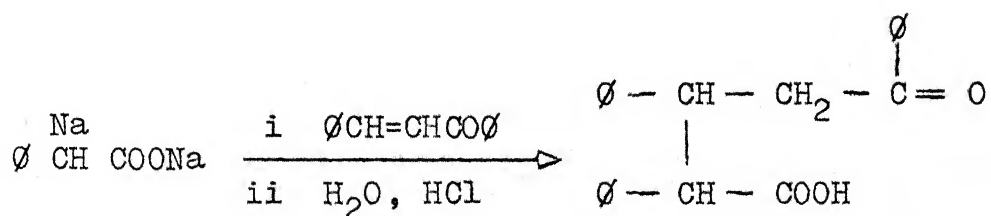
Chalcone is transformed into 3-phenylindan-1-one (50%) when it is heated with polyphosphoric acid<sup>9</sup>:



Two side reactions, one leading to the formation of dihydro-chalcone and the other to an aromatic acid (formed by  $\alpha$ -carbonyl cleavage) have been observed.<sup>9</sup>

With Phenylacetic Acid:

Chalcone reacts with disodiophenyl acetic acid (prepared by the interaction of the acid with two equivalents of sodium amide in liquid ammonia) to give the corresponding keto acid<sup>10</sup> in excellent yield:

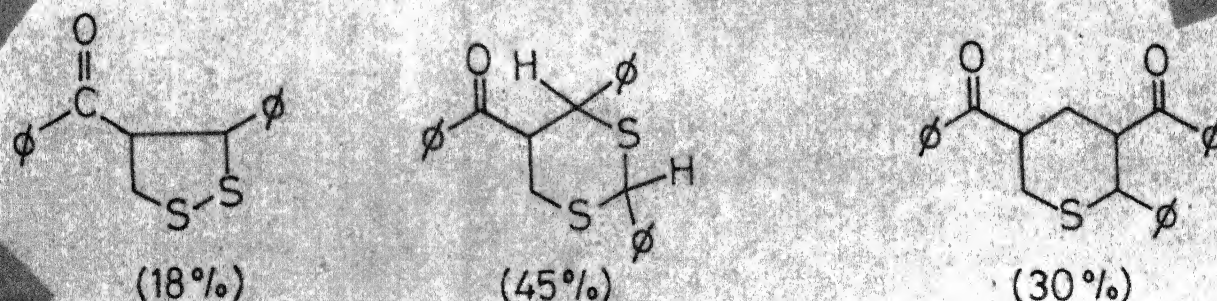


With Sodium Bisulphite:

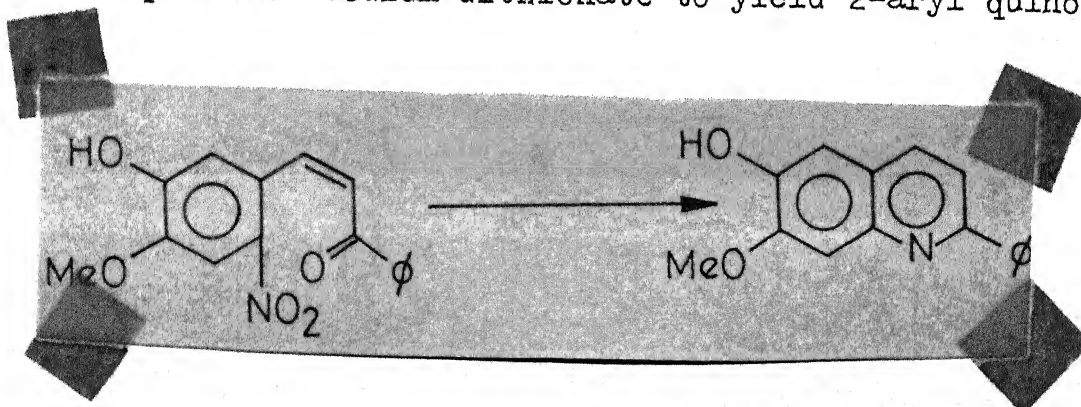
2'-Hydroxychalcone is reported<sup>11</sup> to react (at 135°) with bisulphite to yield 21% of 2 (o-hydroxybenzoyl)-1-phenylethane sulphonic acid. 4'-Hydroxy-2'-methoxychalcone and 4'-hydroxy-3,3',4-trimethoxychalcone react with sodium bisulphite in an analogous fashion.

With Alkali Sulphide:

Chalcone hydrosulphide,<sup>12</sup>  $\phi\text{CH} = \text{CH}-\phi-\text{C}(\text{OH})-\text{SH}$  is produced when chalcone, in alcoholic potassium hydroxide is saturated with hydrogen sulphide. Dibenzalacetophenone disulphide,<sup>12</sup> however, results when chalcone and NaSH are treated in an alcoholic solution. Trans- $\alpha$ -bromomethylchalcone reacts with sodium hydrogen sulphide to yield the following products<sup>13</sup>:



6-Nitrochalcones undergo reductive cyclisation<sup>14</sup> with ammonium sulphide or sodium dithionate to yield 2-aryl quinolines:



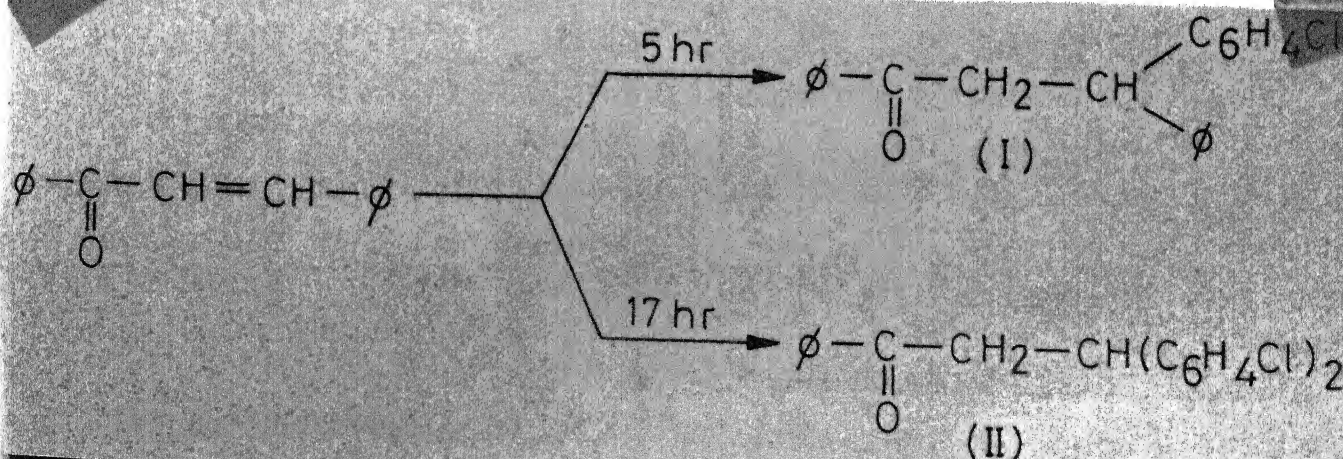
With Anhydrous Aluminium Chloride:

Chalcone undergoes cyclisation with fused  $\text{AlCl}_3$ -NaCl to yield the 3-phenyl-1-indanone (60%).<sup>15</sup>



Under Friedel-Crafts conditions, chalcones in general yield different products depending upon several factors,<sup>16,17</sup> for example, time and temperature of reaction and steric influences. Chalcone on treatment with anhydrous  $\text{AlCl}_3$  in benzene yields  $\beta\beta'$ -diphenyl propiophenone (90%)<sup>17</sup> together with small amounts of 3-phenyl hydrindone<sup>17</sup> and cis-chalcone.<sup>18</sup> While on the other hand  $\alpha$ -methyl and  $\alpha$ -phenyl chalcones, under similar conditions yield the corresponding hydrindones. In these two cases apparently the steric effects<sup>17</sup> are responsible for the formation of hydrindone in preference to the addition product. There are also reports about the preparation of  $\beta\beta'$ -disubstituted propiophenones<sup>19</sup> and/or of substituted hydrindones<sup>20</sup> based on the aforesaid reaction. Aluminium chloride is also reported<sup>21</sup> to bring about partial demethylation. Thus 2'-hydroxy-4',6'-dimethoxy chalcone, under the above conditions, yields 2',4'-dihydroxy-6'-methoxy-chalcone.

Furthermore, chalcone and chlorobenzene react in presence of  $\text{AlCl}_3$  to give products as indicated<sup>22</sup>:



attracted to the  $\beta$ -carbon atom. When the reaction period is

prolonged, then the replacement of the phenyl group by chlorophenyl residue takes place at the  $\beta$ -carbon atom, leading to the formation of II.

With Nitrosoyl Chloride<sup>23</sup>:

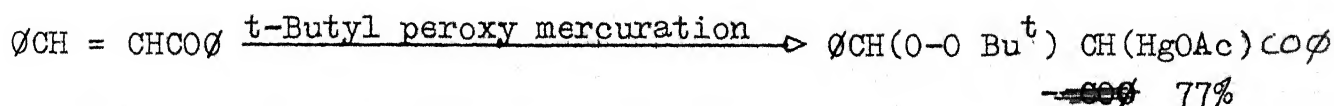
At room temperature chalcone adds to a molecule of nitrosoyl chloride and a good yield of the adduct is obtained.

With Sodium Amide<sup>24</sup>:

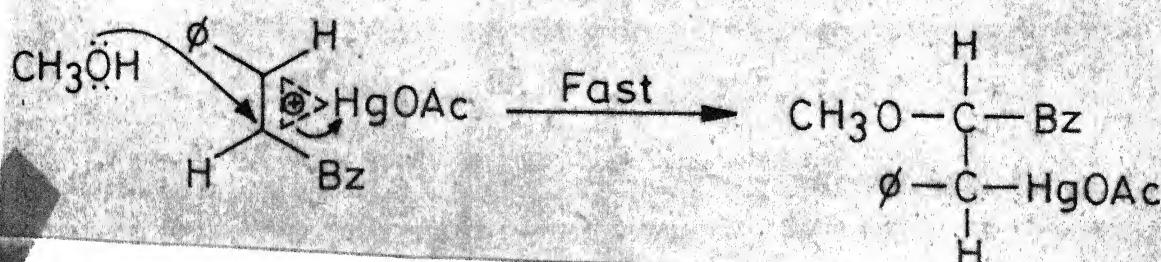
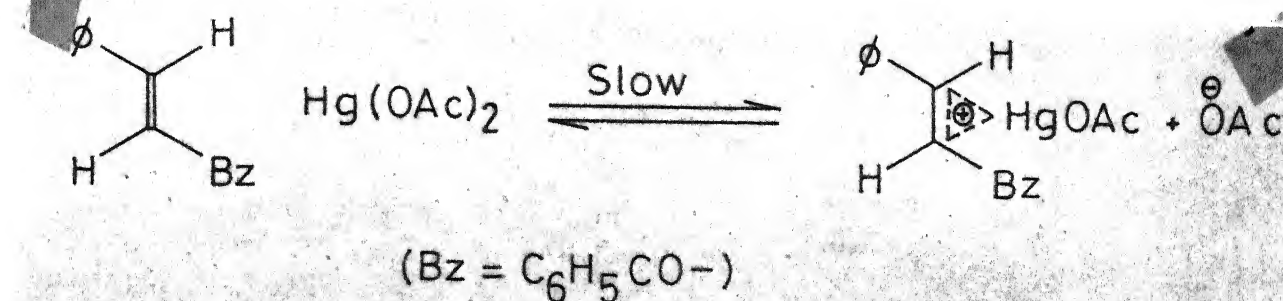
2',4,4'-Trimethoxychalcone on treatment with sodium amide in refluxing toluene undergoes molecular cleavage to yield 1-amido-2(p-methoxyphenyl) ethylene and 1,3-dimethoxybenzene.

With Mercury Salts:

Mercury chloride and mercury bromide are reported<sup>25</sup> to yield addition products with chalcone.  $\alpha$ -Mercuration occurs<sup>26</sup> when chalcone is reacted with mercuric acetate in presence of *t*-butyl hydroperoxide and perchloric acid.



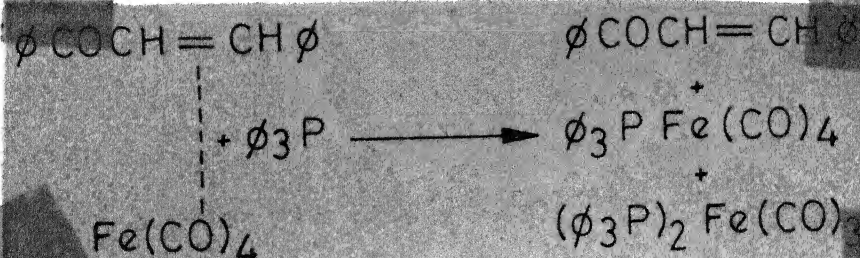
A parallel pattern of behaviour is exhibited by chalcone in methoxymercuration reaction.<sup>26</sup> The kinetics of methoxymercuration of substituted chalcones has been studied.<sup>27</sup> The following mechanism has been postulated<sup>27</sup> for the above-mentioned reaction:



#### With Iron Carbonyl:

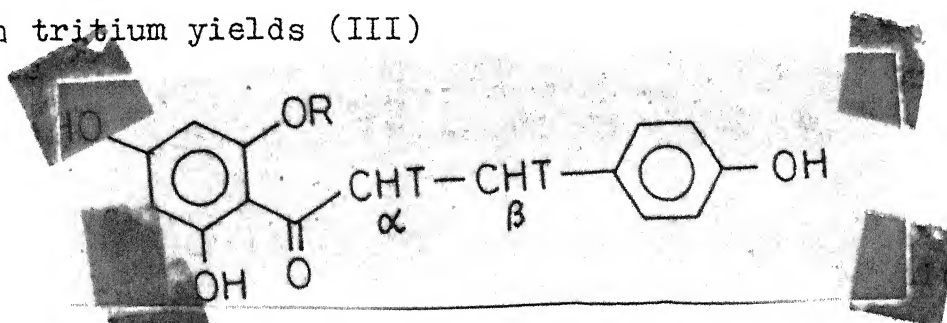
The preparation of several iron carbonyl (tri- and tetra-) complexes of ferrocene analogues of chalcone has been described<sup>28</sup>. The introduction of the iron carbonyl moiety is reported to interfere with the conjugation in the molecule of ferrocene analogue of chalcone.

Iron carbonyl,  $\text{Fe}_2(\text{CO})_9$  reacts with chalcone to yield a complex. The iron-carbonyl chalcone complex reacts with triphenylphosphine<sup>29</sup> in accordance with the reaction:



With Tritium<sup>30</sup>:

Hydrogenation of 2'-D-glucosyl-4,4',6'-trihydroxychalcone with tritium yields (III)



The incorporation of tritium in the dihydro-compound (III) is reported<sup>30</sup> to be of the order of 60% at the  $\alpha$ -carbon atom (with respect to the carbonyl group) and 15-20% at the  $\beta$ -carbon atom respectively.

With Heavy Water<sup>31</sup>:

The  $\alpha$ -hydrogen of chalcone does not exchange for deuterium when it is heated with heavy water-dioxan in the presence of a basic catalyst.

With Deuterioethanol:

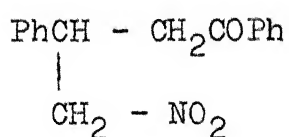
Chalcone is reported<sup>32</sup> to undergo base catalysed deuteration with deuterioethanol, to yield the  $\alpha$ -deuterioketone (42%).

With Benzene and Nitroparaffins:

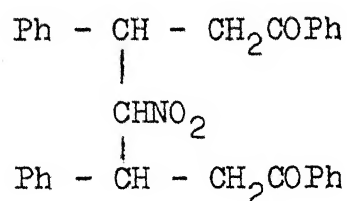
$\alpha$ -substituted chalcone derivatives are reported<sup>33</sup> to undergo addition reaction with benzene in the presence of palladium (II) acetate.

Chalcones react with nitroparaffins,<sup>38,39</sup> e.g., nitromethane,<sup>34-37</sup> 1-(and -2) nitropropanes<sup>35</sup> and gem-dinitroalkanes,<sup>40</sup> to give Michael type addition compounds, generally in excellent yields.<sup>38</sup> This reaction has been accomplished under the influence of basic catalysts, namely alcoholic ammonia,<sup>34</sup> calcium hydride<sup>35</sup> in methanol or pyridine.<sup>40</sup>

The primary addition product of chalcone and nitromethane,<sup>36</sup> for example, is 4-nitro-1,3-diphenylbutan-1-one (IV), further reaction yielding the bis adduct (V)



(IV)



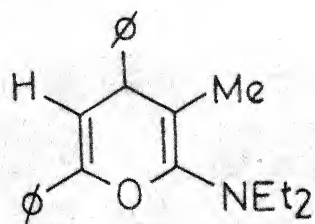
(V)

#### With Diazomethane:

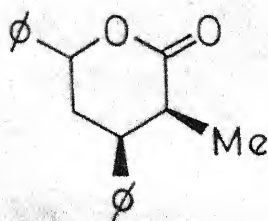
Chalcone reacts additively with diazomethane to yield two isomeric pyrazolines,<sup>41</sup> which upon heating pass into cyclopropane derivative.<sup>42</sup> Homologation of chalcone, however, occurs,<sup>43</sup> without significant pyrazoline formation, if the reaction with diazomethane is performed in the presence of fluoroboric acid.

#### With 1,1-Diethylaminoprop-1-yne:

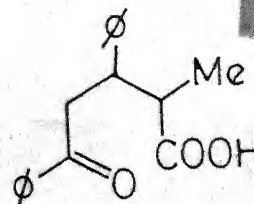
Chalcone is reported<sup>44</sup> to react with 1,1-diethylaminoprop-1-yne to yield a pyran derivative (VI) which on hydrolysis gives the lactone (VII) and keto acid (VIII).



(VI)



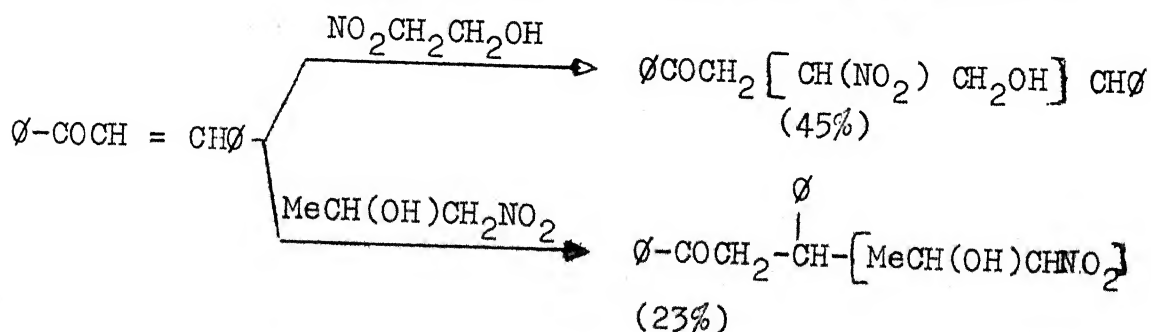
(VII)



(VIII)

### With Alcohols:

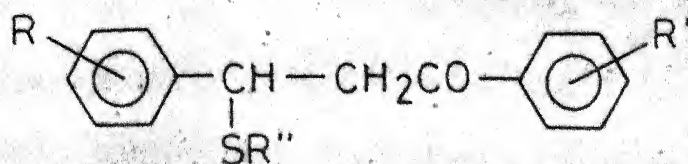
(a) Chalcones react with nitroethyl- and nitro-isopropyl alcohols in liquid ammonia, according to the scheme<sup>45</sup>:



(b) The selective hydrogenation of chalcone has been achieved<sup>46</sup> by using ethylene glycol in the presence of a catalyst,  $\text{RuCl}_2 \cdot \text{PPh}_3$ . The yield of  $\alpha, \beta$ -saturated ketones<sup>46</sup> thus range between 77 to 99%. As an extension of this reaction, chalcone has been used as a solvent-hydrogen acceptor<sup>47</sup> in the presence of  $\text{RuCl}_2 \cdot \text{PPh}_3$  for effecting dehydrogenation of  $\alpha$ -ethylenic alcohols and glycols.

With Thiols<sup>48,49</sup>:

Excellent yields of keto sulphides (IX) are reported<sup>48</sup> to be obtained when substituted chalcone and the hydrochlorides of 2-diethylaminoethyl and 3-diethylaminopropyl mercaptans are allowed to re



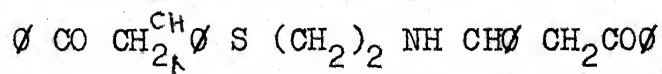
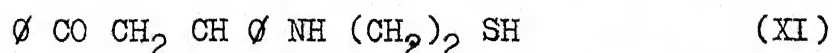
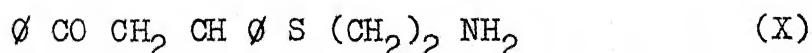
(IX)

R'' = Et<sub>2</sub>NCH<sub>2</sub>CH<sub>2</sub>-;

Et<sub>2</sub>NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-

Pentanethiol, benzene thiol and toluene thiol likewise react with ferrocene analogue of chalcone to give their corresponding adducts.<sup>50</sup>

2-Aminoethanethiol,<sup>51</sup> however, reacts with chalcone to yield either a mono-adduct ((X) and (XI)) or the bis compound (vide infra) depending upon the molar proportion of the reactants used:



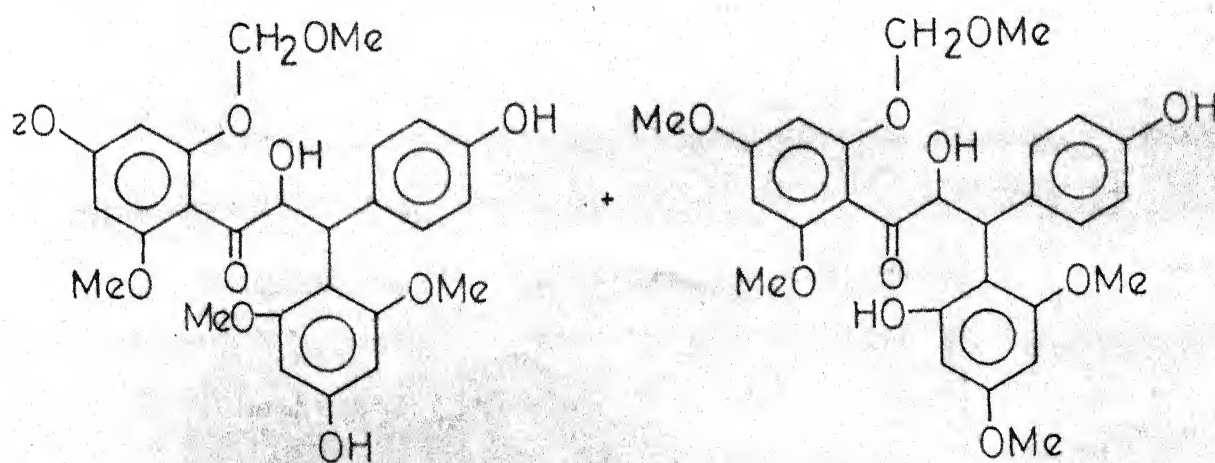
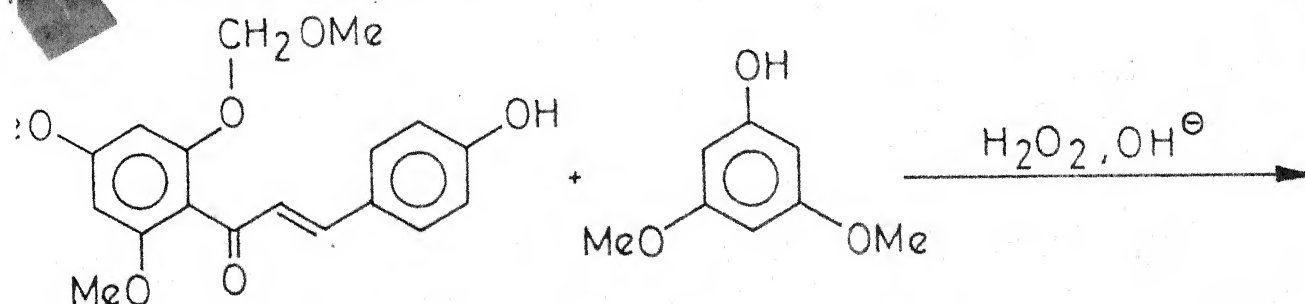
With Selenols:

Arylselenols add readily to chalcone in ethanol, in the absence of a catalyst. The yield of the product, viz., ketosele-nides<sup>52</sup> vary from 44 to 80%.



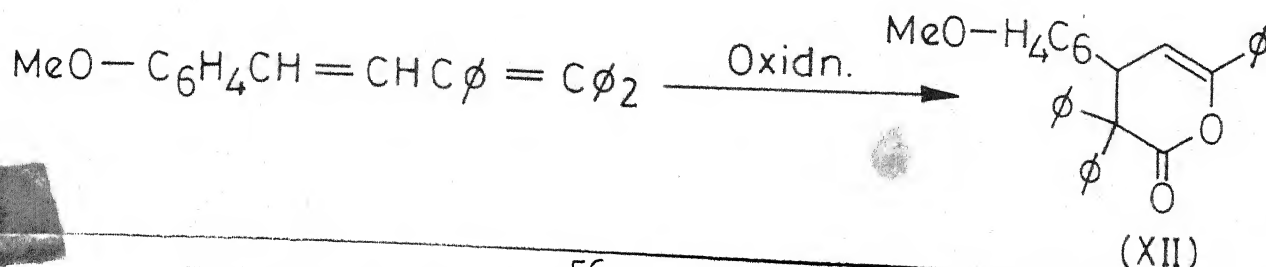
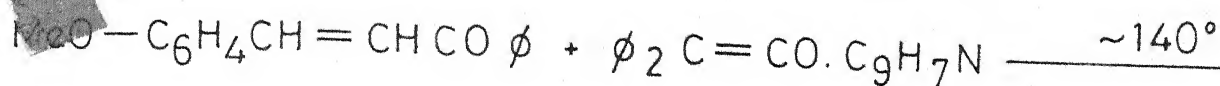
With 3,5-Dimethoxyphenol<sup>53</sup>:

Substituted chalcone is reported<sup>53</sup> to undergo  $\beta$ -coupling with 3,5-dimethoxyphenol, in the presence of alkaline hydrogen peroxide, to yield the two structural isomers of 3,3-diaryl-2-hydroxypropio-phenone:

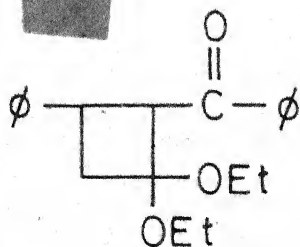


ketenes:

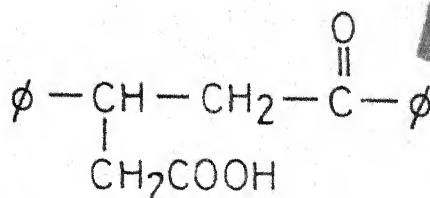
$\delta$ -Lactones<sup>55</sup> are obtained from chalcones by their interaction with diphenylketene quinoline, followed by an oxidative step. The preparation of  $\alpha, \alpha$ -diphenyl- $\beta$ -methoxyphenyl- $\gamma$ -benzoyl butyric lactone (XII) is illustrated<sup>55</sup>:



Chalcone is reported<sup>56</sup> to react with one equivalent of ketene acetal to yield 1,1-diethyl-2-benzoyl-3-phenylcyclo-butane (XIII) which may be hydrolysed to 3- $\beta$ -phenyl- $\gamma$ -benzoyl butyric acid (XIV).

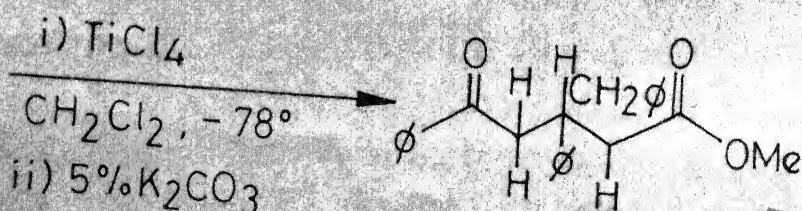
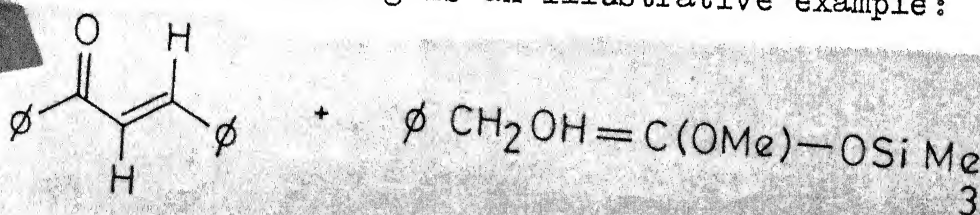


(XIII)



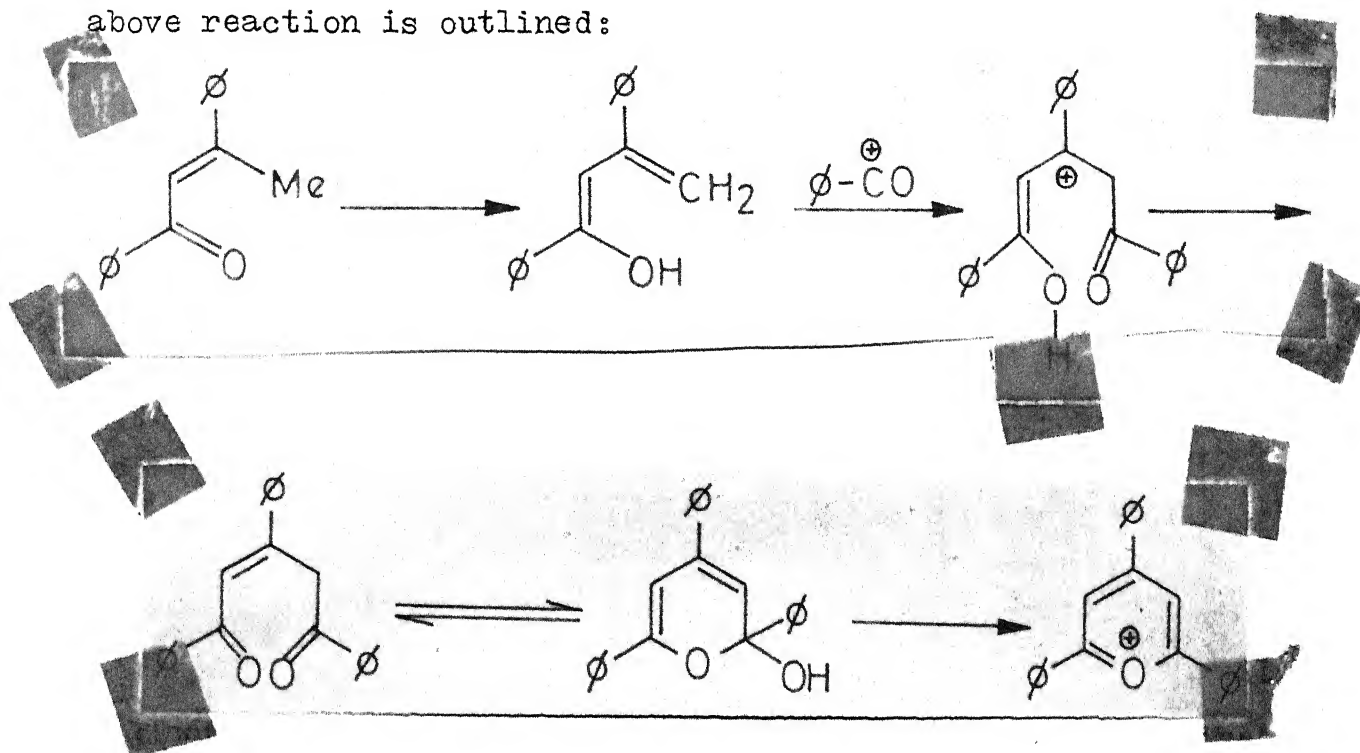
(XIV)

The Michael type reaction of chalcone with o-silylated ketene furnishes the corresponding  $\delta$ -keto esters<sup>57</sup> in good yields. The following is an illustrative example:



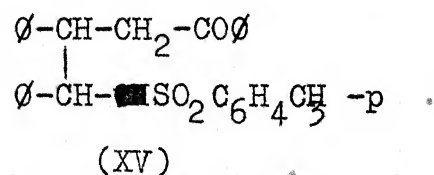
With Benzoyl Chloride:

Pyrylium salts<sup>58</sup> are formed when  $\beta$ -methyl chalcones, in acetic acid, are reacted with benzoyl chloride in the presence of a Lewis acid. One of the possible mechanisms suggested<sup>58</sup> for the above reaction is outlined:



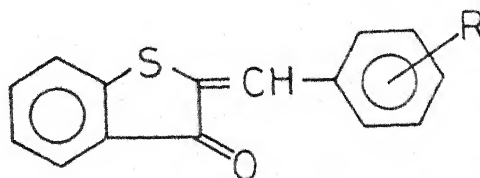
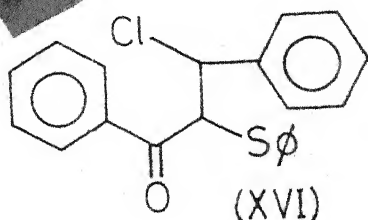
With Benzyl-p-tolyl Sulphone:

In the presence of sodium ethoxide, chalcone is reported to condense with benzyl-p-tolyl sulphone to yield a product<sup>59</sup> (XV, ~15%) which exists in two isomeric forms:



### With Sulfenyl Compounds:

Chalcones react with phenyl sulfenyl chloride<sup>60</sup> in acetic acid medium to furnish an adduct (XVI) or thioaurones (XVII)



R = Me, Cl  
 R = o-OH; o-Cl; o-MeO;  
p-Me<sub>2</sub>N and p-NH<sub>2</sub>SO<sub>2</sub>

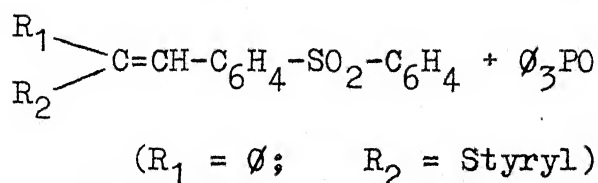
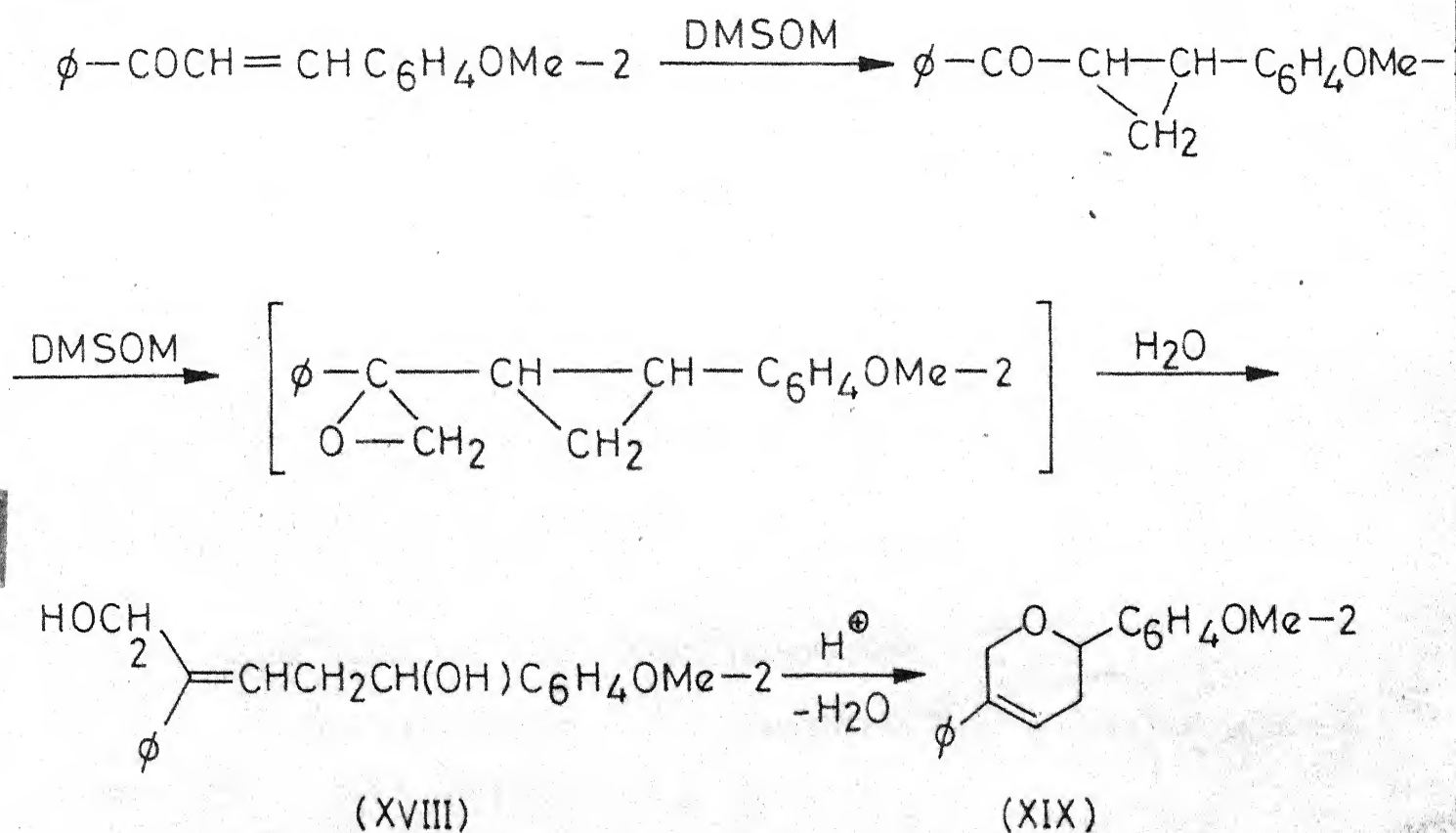
1-(Phenylsulfinyl)-2,4-diphenyl-3-buten-2-ol<sup>61</sup> is preparable by the interaction of chalcone with  $\text{OS(O)CH}_3$  in the presence of sodium amide in liquid ammonia.

### With Dimethyl Sulphonium and Sulphoxonium Methylides:

Dimethyl sulphonium methylide is reported<sup>62</sup> to react with chalcone to yield the corresponding oxirane by the selective addition of methylene to carbonyl group:

on the other hand, trans chalcone reacts with dimethyl sulfoxonium methylide (DMSOM) leading to the formation of trans 1-phenyl-2-benzoylcyclopropane.<sup>62</sup> 2-Methoxychalcone, on prolonged treatment

with DMSOM, however, yields (XVIII) which cyclises to pyran derivative<sup>64</sup> (XIX) in the presence of acid. Thus:

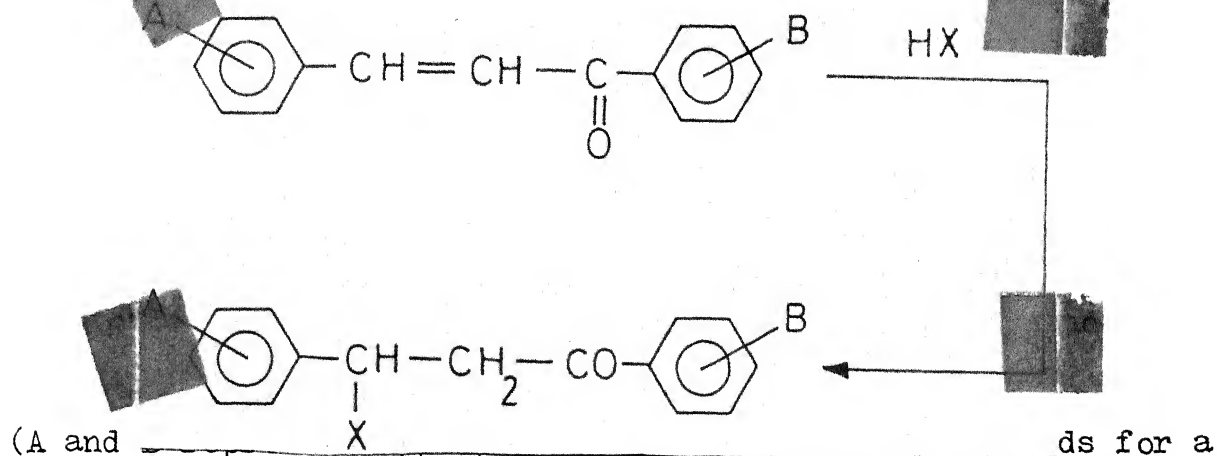


#### With Nitron:

C, N-Diphenylnitron and N-methyl-C-phenylnitron are reported<sup>66</sup> to undergo 1,3-dipolar cyclo-addition with p-substituted chalcone, to yield the corresponding isoxazolidine ring system.

### With Nitrogen Heterocycles:

Chalcones have been reacted with several nitrogen heterocycles, for example, piperidine,<sup>67</sup> morpholine,<sup>67</sup> N-bromo-morpholine,<sup>68</sup> piperazine,<sup>69</sup> indoles<sup>70,71</sup> and azoles<sup>72</sup> to yield the corresponding Michael adducts. The following serve as examples<sup>67</sup>:

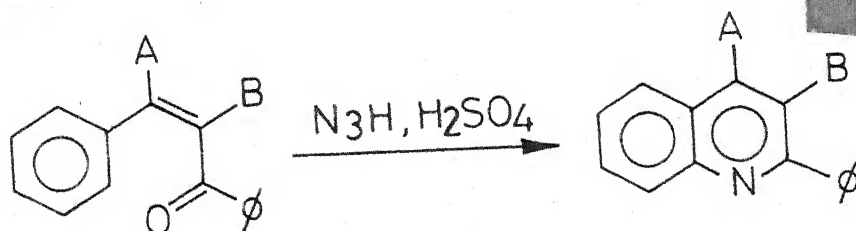


The addition compounds are unstable and break up into its constituents in hot water.

A Michael adduct is formed by the interaction of chalcone with 3,5-dimethyl-4-nitroisoxazole. The adduct on reductive cyclisation is reported to yield<sup>73</sup> the corresponding azepine derivative.

### With Hydrazoic Acid:

The Schmidt reaction on highly hindered cis-chalcone is reported<sup>74,75</sup> to yield quinoline derivatives.

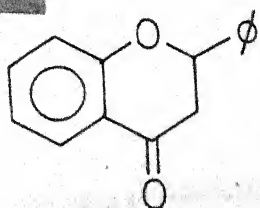


(XX)  $A = B = \phi$ ;

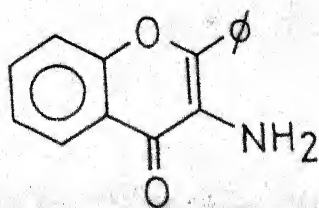
(XXI)  $A = B = \text{Br}$

The kinetics of this reaction has been studied.<sup>76,77</sup>

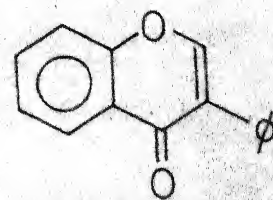
The reaction of hydrazoic acid with 2'-hydroxychalcone has been carried out.<sup>78</sup> The following heterocyclic compounds (XXII-XXVI) have been isolated<sup>78</sup>:



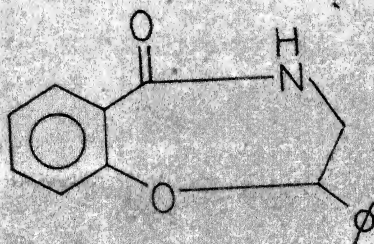
(XXII)



(XXIII)

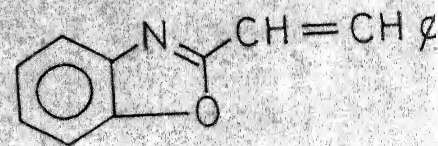


(XXIV)



(XXV)

and



(XXVI)



### With Hydroxylamine:

Chalcone and substituted chalcones react with hydroxylamine hydrochloride to form the corresponding unsaturated ketoximes.<sup>79-83</sup> The ketoximes are reported<sup>79,80,90-93</sup> to undergo a variety of reactions, viz., cyclisations, catalytic hydrogenation, Beckmann rearrangement etc.

3,5-Diphenylisoxazoline is formed<sup>79,80</sup> when chalcone is allowed to react with hydroxylamine in an alkaline medium. It is believed<sup>81</sup> that chalcone syn-oxime is formed in the reaction, which undergoes cyclisation to the corresponding isoxazoline derivative. Chalcones carrying substituents in the 4- and 4'-positions react, under acid conditions, with hydroxylamine hydrochloride to yield isoxazolines and chalcone syn-oximes. On the other hand isoxazolines along with other products are formed under alkaline conditions.<sup>84,85</sup> Isoxazolines (XXVII) derived from naphthalene analogues of chalcone have been secured<sup>86</sup> by their reaction, at a higher temperature, with hydroxylamine in presence of pyridine.

In some cases the formation of isoxazole<sup>82,88,89</sup> and dihydroisoxazole<sup>87</sup> have been reported. The mechanism of isoxazole formation is reported<sup>88</sup> to take place by 1,2-addition.

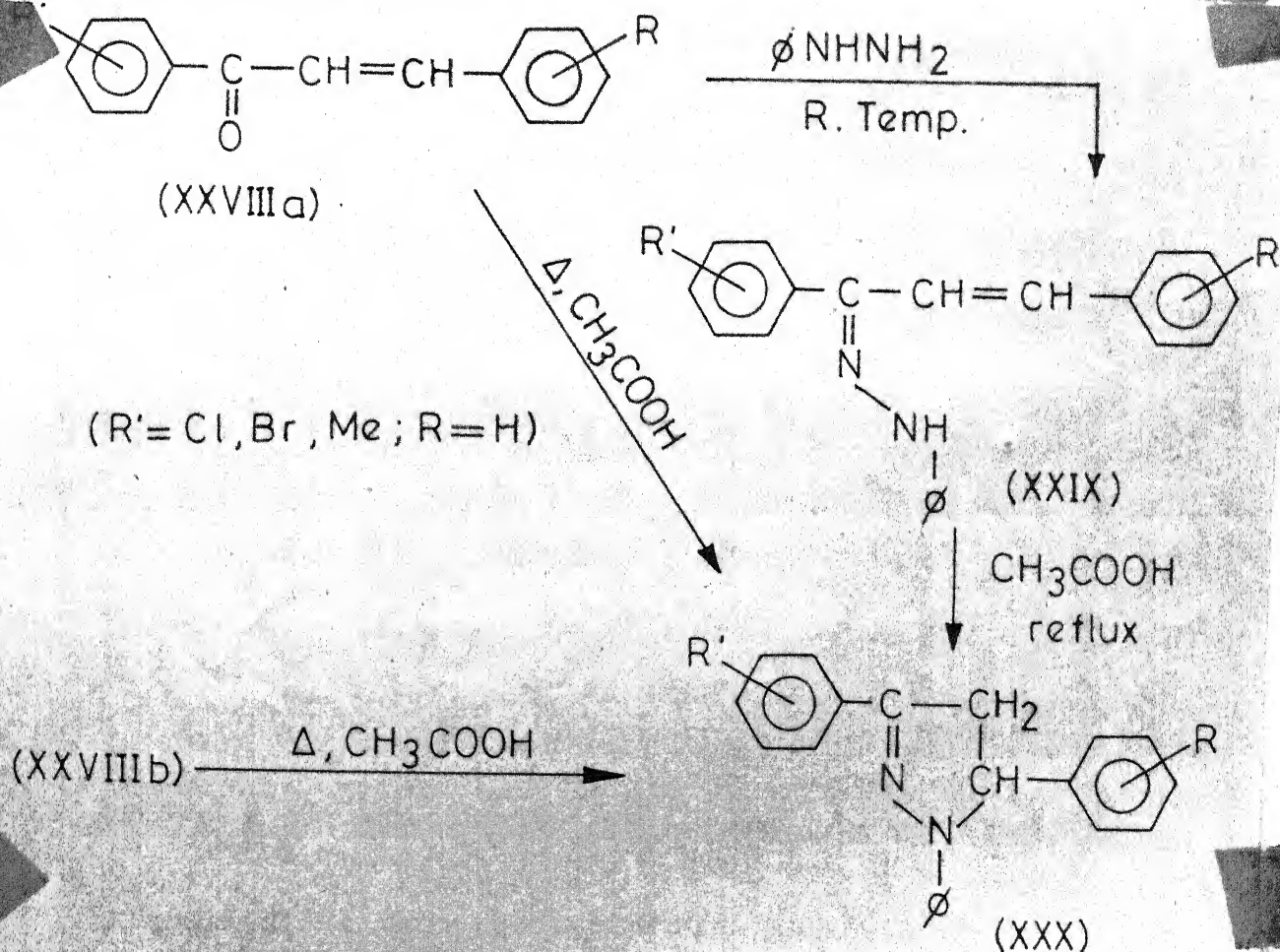
### With Hydrazine:

Hydrazones<sup>94</sup> or pyrazolines<sup>95</sup> are formed by the reaction of chalcone with hydrazine. 4,5-hydro-1H-pyrazoles<sup>87</sup> are, however, produced from 2-hydroxychalcones in the above reaction.

With Phenylhydrazine:

(XXVIII a)

Chalcone (~~XXVIII a~~) react with phenylhydrazine<sup>86,94,96,97</sup> in acetic acid medium to yield the corresponding phenylhydrazones<sup>96,98</sup> (XXIX). The phenylhydrazones can be transformed into 1,3,5-triphenylpyrazolines (XXX) by refluxing these with acetic acid. Some chalcone phenylhydrazones (XXVIII b) are labile and are readily converted to pyrazolines,<sup>96</sup> even at room temperature. If a mixture of chalcone and phenylhydrazine are reacted at higher temperature, the intermediate hydrazone undergoes cyclisation to the corresponding pyrazoline.<sup>86,97</sup>



$\text{R}' = 3\text{-NO}_2, 4'\text{-Acetoxy}; \text{R} = \text{H}$

$\text{R}' = \text{H}; \text{R} = \text{OH}$

With 2,4-Dinitrophenylhydrazine<sup>94,99-103</sup> (DNPH):

The chief advantage of DNPH over phenylhydrazine as a reagent for characterization of chalcones is the ease of separation of the crystalline hydrazones with characteristic sharp melting points. The preparation of some substituted chalcone 2,4-dinitrophenyl hydrazones are reported<sup>99-101</sup> in the literature.

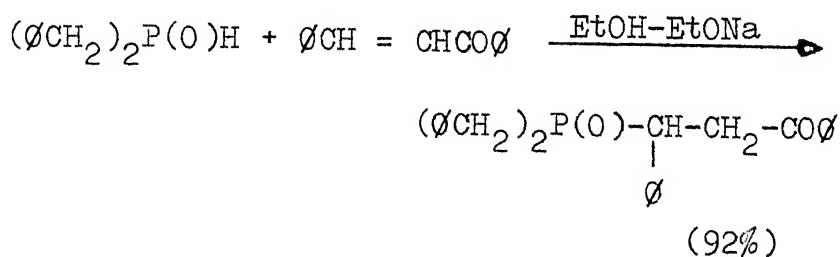
The reactivity of carbonyl group in chalcones, in respect of their formation of 2,4-dinitrophenylhydrazones has been examined.<sup>102,103</sup> The close proximity of the hydroxyl group hinders the reactivity of the carbonyl group on account of chelate formation. Substituents located in the para position with respect to the carbonyl function alter, depending upon their inductive effects,<sup>102,103</sup> the rate of 2,4-dinitrophenylhydrazone formation.

With Hydrazine Derivatives:

Several other hydrazine derivatives,<sup>104-107</sup> viz., <sup>l</sup>1-menthyldrazide<sup>104</sup>; 3,5-dinitro-4-tolyl hydrazine,<sup>105</sup> phenyl sulphonylhydrazide<sup>106</sup> and tosylhydrazine<sup>107</sup> have been used for the characterization of chalcones. One of these derivatives, viz., tosylhydrazone, has an important synthetic application and is used as a starting material for the preparation of substituted cyclopropenes.<sup>107</sup>

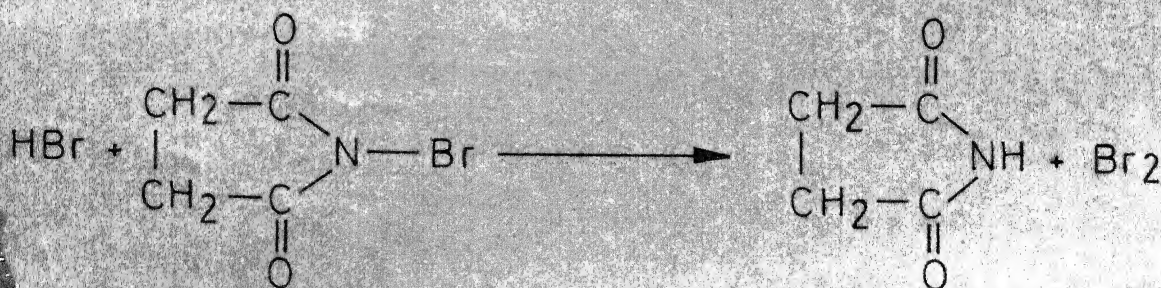
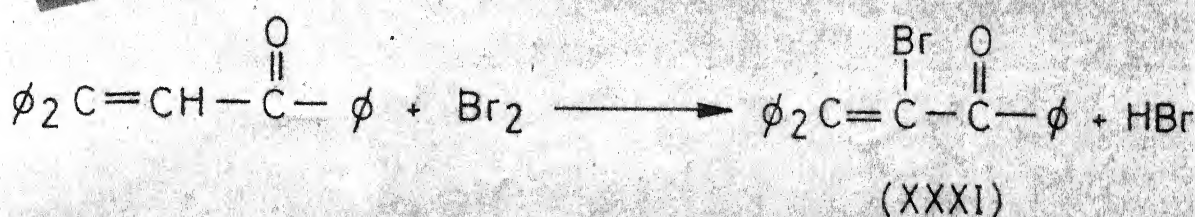
With Disubstituted Phosphine Oxide:

Addition across the olefinic linkage occurs when chalcone is reacted with disubstituted phosphine oxide,<sup>108</sup> under basic conditions, thus:

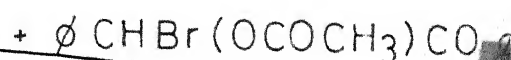
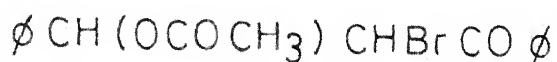


With N-bromosuccinimide<sup>109</sup> (NBS):

$\beta$ -phenylchalcone on treatment with N-bromosuccinimide, gives the  $\alpha$ -bromo derivative (XXXI). The reaction involves a radical mechanism and is initiated by a trace of  $\text{Br}_2$  formed by the decomposition of N-bromosuccinimide.



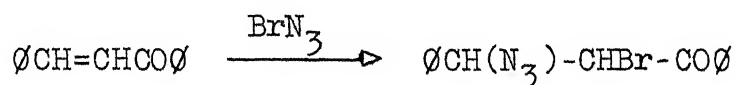
Bromoacetoxylation of several chalcones are reported<sup>110</sup> and is carried out by the reaction of chalcone with NBS in acetic acid.



Apparently  $\alpha$ -bromo- $\beta$ -acetoxy-, and  $\beta$ -bromo- $\alpha$ -acetoxy isomers are produced in the reaction, the relative proportion of which varies from chalcone to chalcone.

With Bromine Azide<sup>111</sup>:

Bromine azide adds very slowly to chalcone in methylene chloride-nitromethane, in the following way:



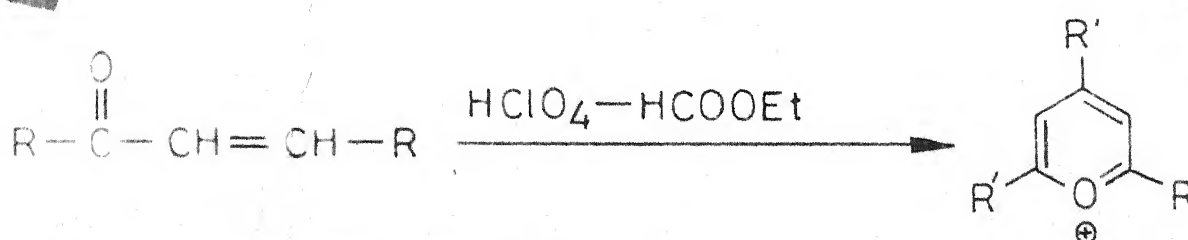
The reaction can, however, be made to go at a reasonable rate by incorporating an acid catalyst.

Pyrolysis:

Pyrolysis of chalcone at about 700° in the presence of aluminium bronze powder, is reported<sup>112</sup> to yield stilbene and 1,4-(m-biphenyl)-benzene.

Autocondensation:

Chalcones are reported<sup>113</sup> to undergo autocondensation in the presence of ethyl formate-perchloric acid to yield 2,4,6-triaryl pyrylium salt in a poor yield (18-48%).



R = R' = Phenyl

= 3,4-(MeO)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>;

= 3,4-(CH<sub>2</sub>O)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>.

Copolymerization of Chalcone/Chalcones AnaloguesWith Styrene:

Substituted chalcone and styrene<sup>114-116</sup> form a copolymer (85% conversion<sup>115</sup>) involving the use of a free radical initiator. The product is described as hard, clear solid polymer, with a heat distortion point of 97° (cf. polystyrene, 78°). A resinous solid, however, is obtained by the ionic interpolymerization of chalcone and styrene with boron trifluoride<sup>119</sup> (at -80°) in methylene chloride.

With Butadiene:

1,3-Butadiene<sup>115</sup> monomer copolymerizes readily with  $\alpha, \beta$  - unsaturated carbonyl compounds in presence of benzoyl peroxide. The carbonyl compounds studied include, chalcone,<sup>115</sup> 2-chloro-chalcone,<sup>118</sup> furfural-acetophenone,<sup>118</sup> furfural-p-chloroacetophenone<sup>118</sup> and some pyridine analogues<sup>119</sup> of chalcone, viz., 2-(3- and 4-) pyridal acetophenones, 2-pyridal-4-chloroacetophenone and 2-pyridal-2'-acetyl-acetophenone. It may, however, be noted that 2-pyridal-4'-amino acetophenone<sup>119</sup> fails to form a copolymer with 1,3-butadiene.

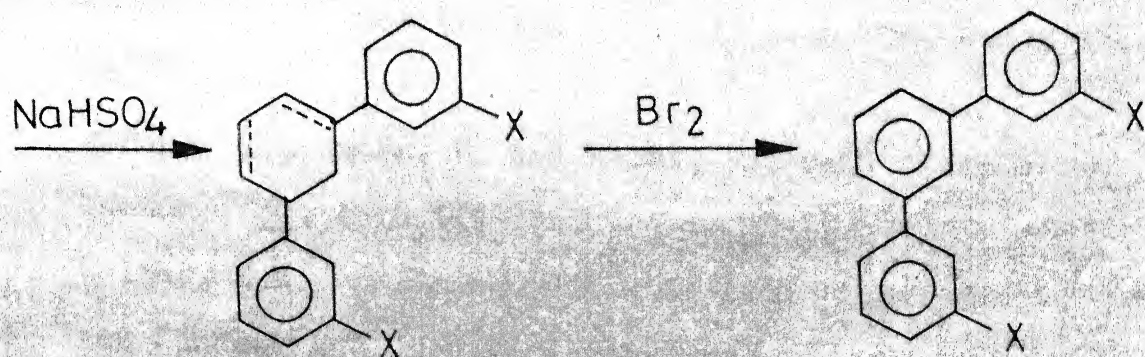
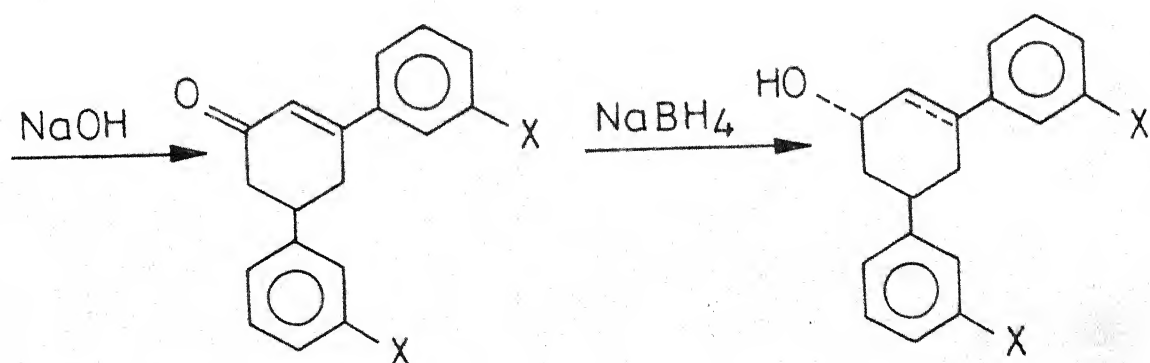
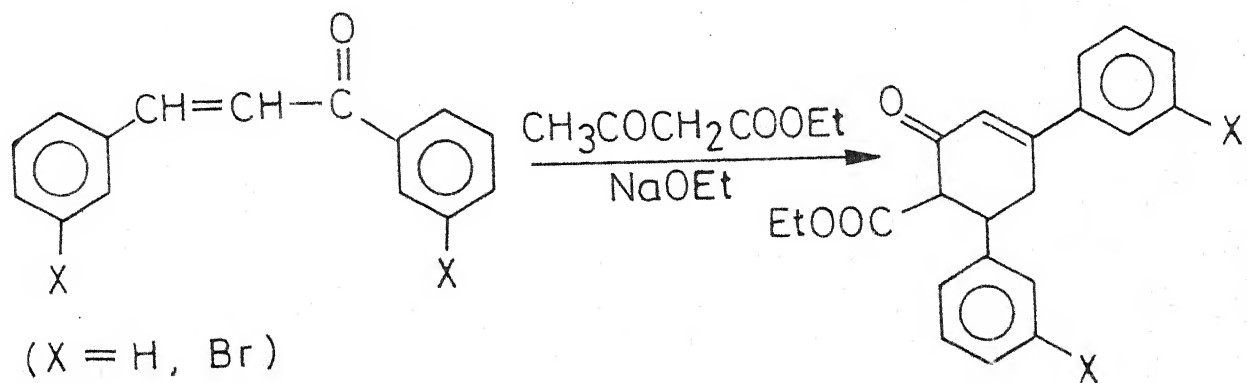
With Acrylonitrile and Isoprene<sup>120</sup>:

Copolymers derived from acrylonitrile (and isoprene) and pyridine analogues of chalcones are described<sup>120</sup> in literature.

Synthesis of m-polyphenyls<sup>121</sup>:

Chalcone serves as a starting material for the synthesis of m-polyphenyl system. The following sequence of reaction steps<sup>121</sup> are necessary in bringing about the required transformation, taking the synthesis of m-terphenyl as an illustrative example:



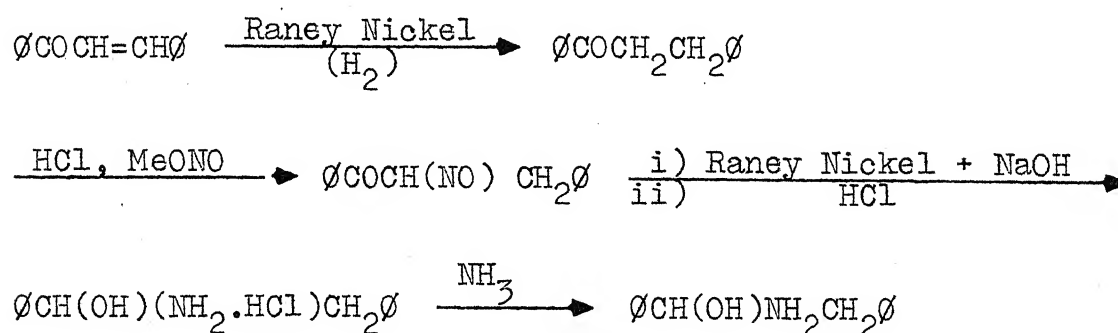


### Synthesis of 1,3-Diphenylglycerol<sup>122</sup>:

Starting with chalcone and taking it through a series of chemical transformations, the two isomers, viz., erythro-erythro and erythro-threo, of 1,3-diphenylglycerol have been isolated<sup>122</sup> and identified.

### Synthesis of Aryl Benzyl Ethanolamines:

The title compounds have been obtained<sup>123</sup> by the following series of reactions. Thus,



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CHAPTER - 8

## PHOTOCHEMISTRY OF CHALCONES AND THEIR DERIVATIVES

Photochemistry of Chalcones.....	194
Photochemical Dimerization.....	195
Photochemistry of Chalcone Derivatives	
Flavanone.....	197
Chalcone Epoxides.....	197
Chalcone Semicarbazones.....	198
References.....	198

Photochemistry of Chalcones:

Photoisomerization of trans-chalcone,<sup>1</sup> trans-2-hydroxy-chalcone<sup>2</sup> and other substituted chalcones,<sup>3,4</sup> and heterocyclic analogues of chalcones<sup>5</sup> into their corresponding cis-isomers has been described in the literature. Cis-2-methoxychalcone is convertible to cis-2-hydroxychalcone (photochemical demethylation)<sup>2</sup> by prolonged irradiation to sunlight. Some chalcones, on the other hand, have a great tendency to undergo resinification,<sup>6</sup> when irradiated either in the solid state or solution, viz., 4,4'-dimethyl (and 4,4'-dimethoxy) chalcones. The solid state photochemistry of some 2'-nitrochalcones has been studied.<sup>7</sup> Various parameters seem to govern the specific pathway followed by the photochemical reaction, viz., molecular conformation and its retention and the molecular packings.

### Photochemical Dimerization:

Photochemical dimerization is reported to occur in the case of several chalcones, viz., chalcone,<sup>6,8</sup> 4'-methyl-chalcone,<sup>6</sup> 4-methoxychalcone<sup>10</sup> and thiophene analogue<sup>11</sup> of chalcone. Dimerization, however, does not take place with chalcone, or 4-methoxychalcone, if these are irradiated in presence of uranyl chloride.<sup>12</sup> Cyclobutane type of structure<sup>6,8</sup> (vide infra) has been assigned to chalcone dimers. These results have been arrived at on the basis of data obtained by physical<sup>8,9</sup> and chemical methods.<sup>6,8,10</sup>

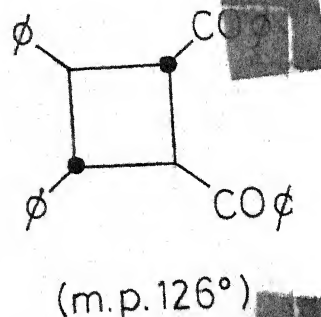
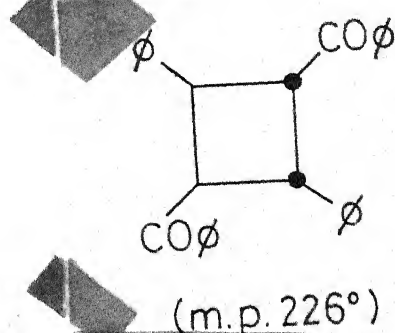
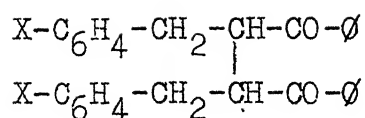
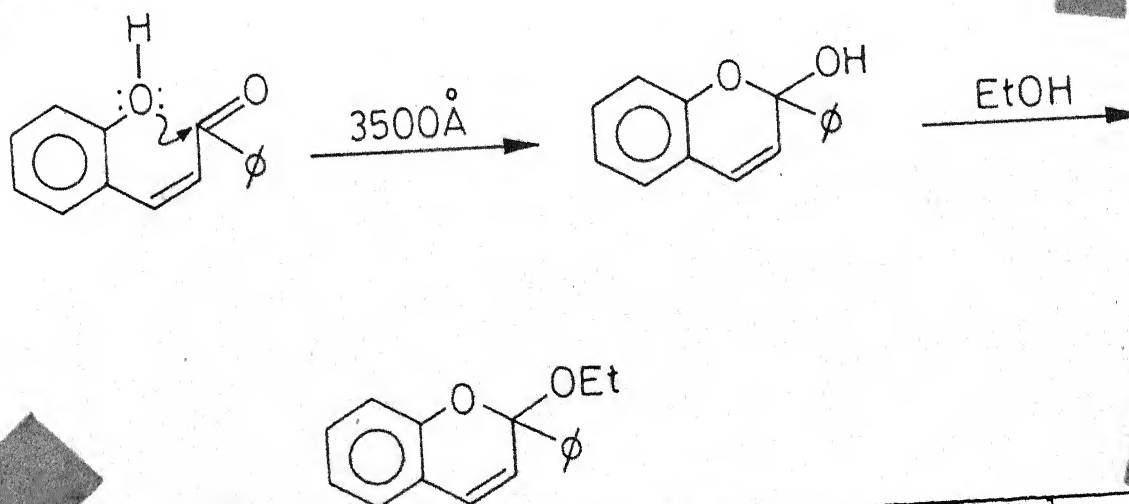


Photo induced dimerization of 4-methoxychalcone is reported<sup>13</sup> to take place with the aid of 4,10-dihydroanthracene. Two types of dimerides,<sup>13</sup> viz., head-tail and head-head orientations are produced, when the photo-reaction is carried out in ethanol and acetonitrile respectively. Chalcone dimers, of the following structure have been obtained<sup>14</sup> in high yield by the photolysis of a solution of chalcone under appropriate conditions<sup>15</sup>:



(X = H; 4-OMe or 4-Cl).

Photolysis of 2-hydroxychalcone, in ethanol, is reported<sup>16</sup> to yield 2-ethoxy-flav-3-one (96%) and a very small amount (1%) of flavone, according to the reaction:



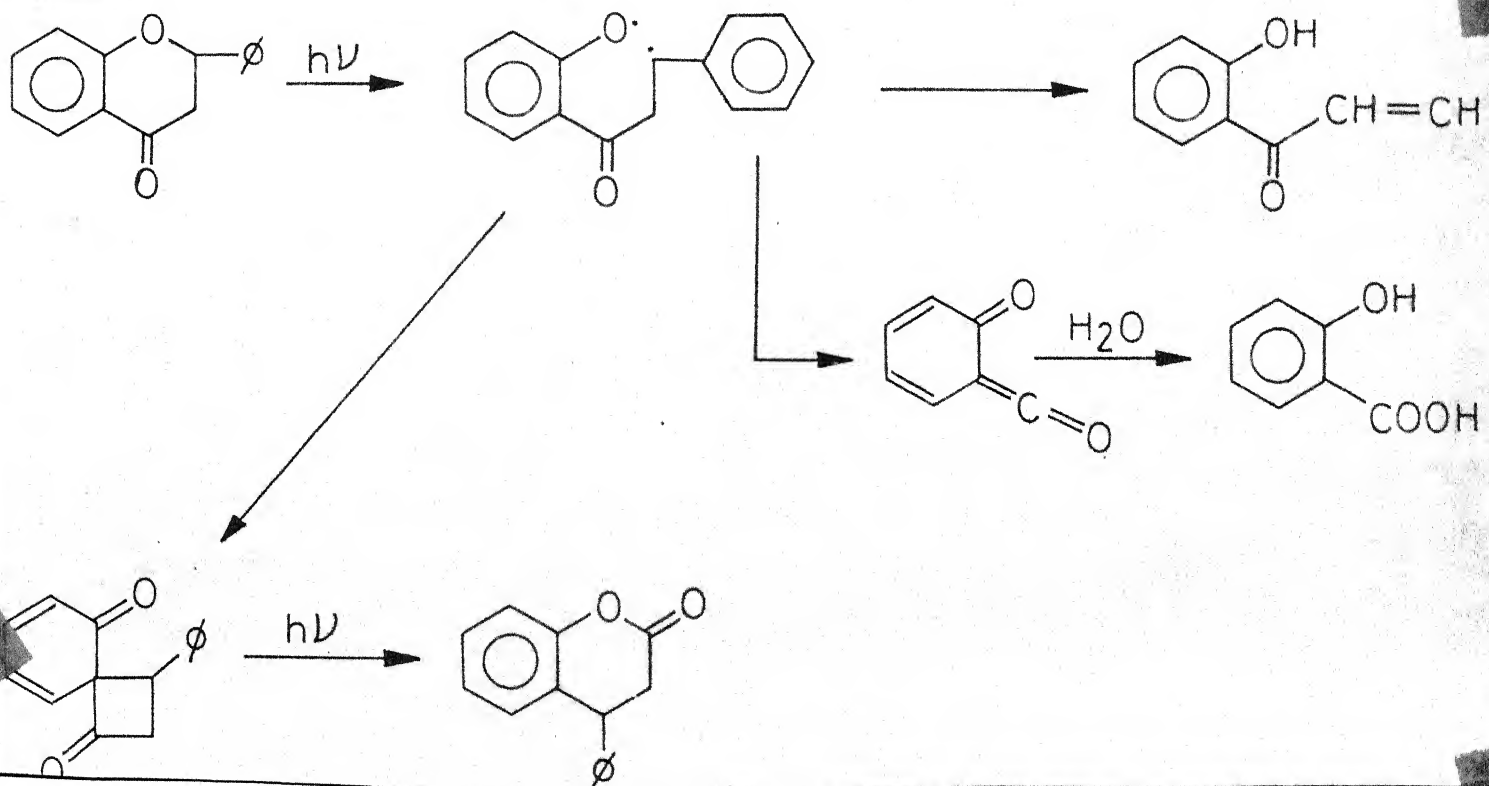
Chemical oxidation by visible light has been reported<sup>17</sup> in the case of 2'-hydroxy-4',6',3,4-tetramethoxychalcone leading to the formation of 5,7,3',4'-tetramethoxyflavanonol. The 3-hydroxylic function in the flavanonol is assumed to arise from the hydroxylic radical generated by the photolysis of aqueous-methanol, used as the solvent.



## Photochemistry of Chalcone Derivatives

### Flavanone:

UV irradiation of flavanone is reported<sup>18</sup> to yield three products, viz., 2'-hydroxychalcone (20%), 4-phenyl-dihydro-coumarin (13%) and salicylic acid (4%). The mechanism<sup>18</sup> of the reaction is as follows:



Chalcone epoxides are reported<sup>19</sup> to undergo photo-oxidative cleavage yielding a mixture of acid and aldehyde. Thus, for example, 2',3,4,4'-tetramethoxychalcone epoxide<sup>19</sup> yields veratraldehyde and 2,4-dimethoxybenzoic acid, under these conditions. According to another report<sup>20</sup> trans chalcone epoxide and trans 2-methoxychalcone epoxide on irradiation yield

dibenzoylmethanes, trans-cis isomerization and fragmentation via acyl carbene intermediates. Evidence has been put forward<sup>21</sup> about the intermediacy of dioxoles when substituted chalcone <sup>epoxides</sup> / are photolysed. The dioxoles are produced by the cleavage of the  $C_{\alpha} - C_{\beta}$  oxirane bond, leading to the formation of carbonyl ylides, which subsequently rearrange to dioxoles.

#### Chalcone Semicarbazones:

Some of the chalcone semicarbazones are reported<sup>22</sup> to exhibit noticeable photochemical isomerism. Examples are: p-methylchalcone and p-methoxy-p'-methylchalcone.<sup>22</sup>

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CHAPTER - 9POLAROGRAPHIC STUDIES OF CHALCONES, CHALCONE ANALOGUES AND  
THEIR DERIVATIVES

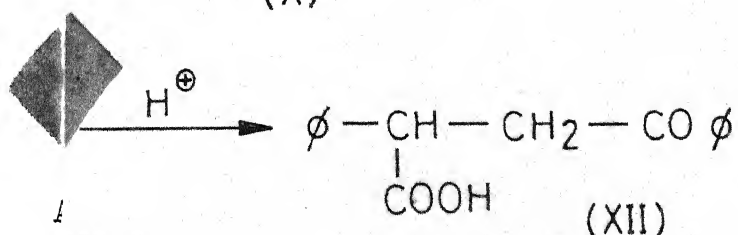
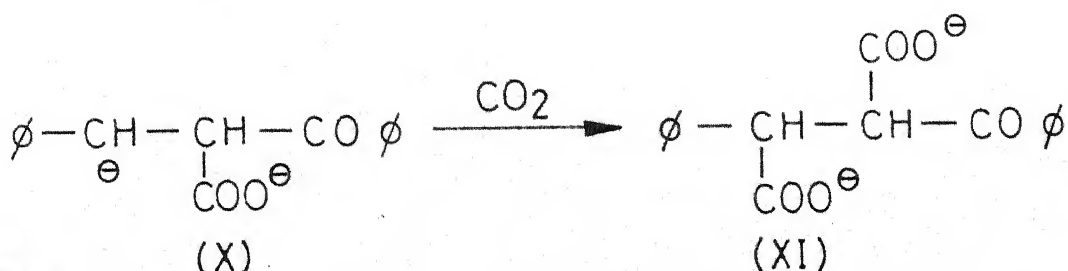
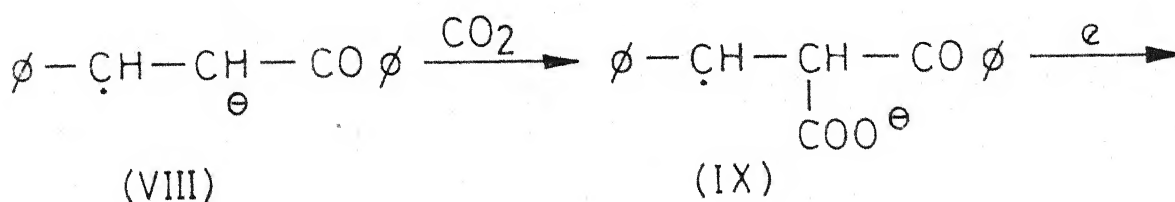
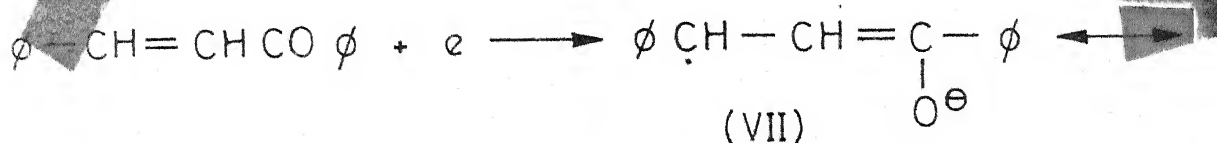
Polarographic Reduction of Chalcone.....	200
Mechanism.....	201
Polarographic Reduction of Chalcone in DMF.....	201
Mechanism.....	202
Substituent Effects on Polarographic Reduction of Chalcones...	204
Polarographic Reduction of Chalcone Analogues.....	205
Polarographic Analysis of 2'-hydroxychalcone-flavanone mixture	205
Polarographic Conversion of 2'-hydroxychalcone to Chromanone..	205
Polarographic Conversion of Chalcone to Chalcone Hydrazone....	206
Polarographic Behaviour of Pyridine Analogue of Chalcone Oxime	206
References.....	206

Polarographic Reduction of Chalcone:

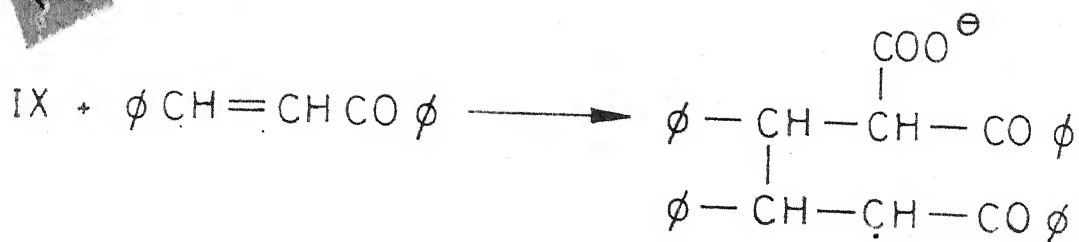
Chalcone undergoes reduction on a dropping mercury electrode yielding a variety of products depending upon the conditions of the experiment. The present picture about the mechanism involved in the formation of these products from chalcone, for example, has emerged as a result of the work of several investigations<sup>1-14,17-19</sup> and is summarized below:



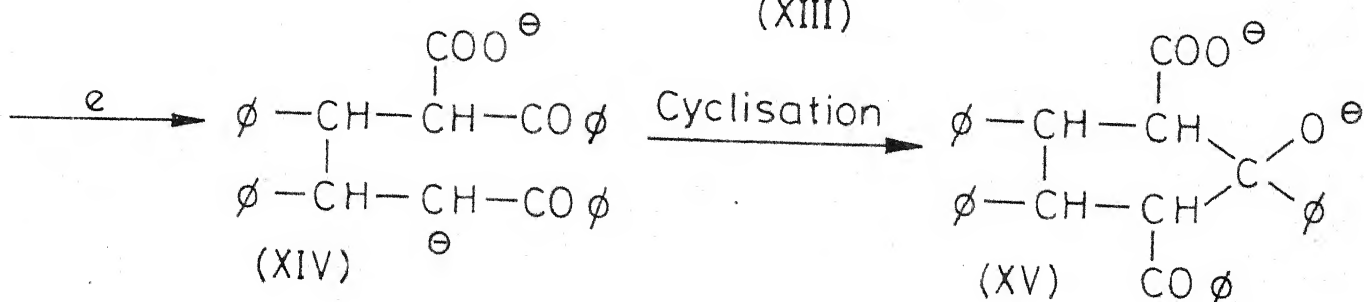
$\beta$ -benzoyl propionic acid (XII) and (XIV) are formed. The mechanism of formation of (XII) can be rationalized<sup>9</sup> as follows:



double bond of another chalcone molecule and then be reduced further to yield finally the dimeric monocarboxylic acid (XVI):

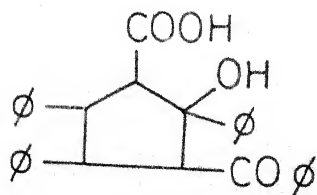


(XIII)



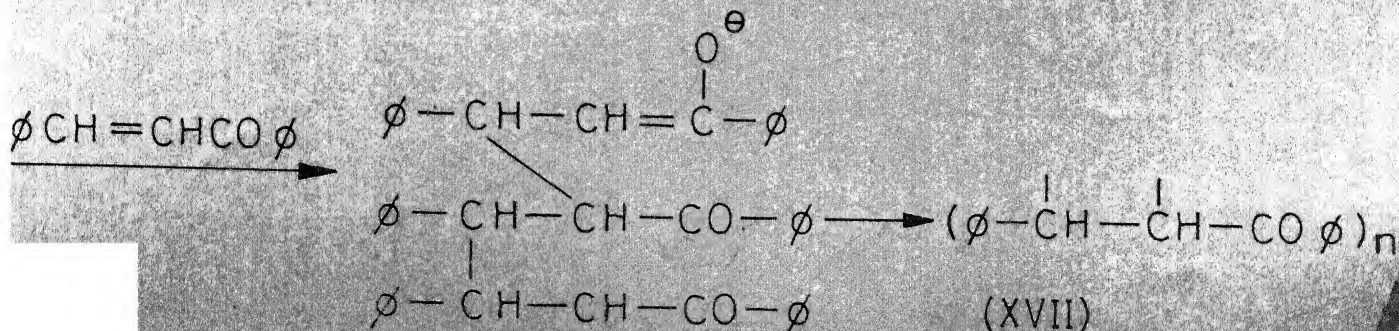
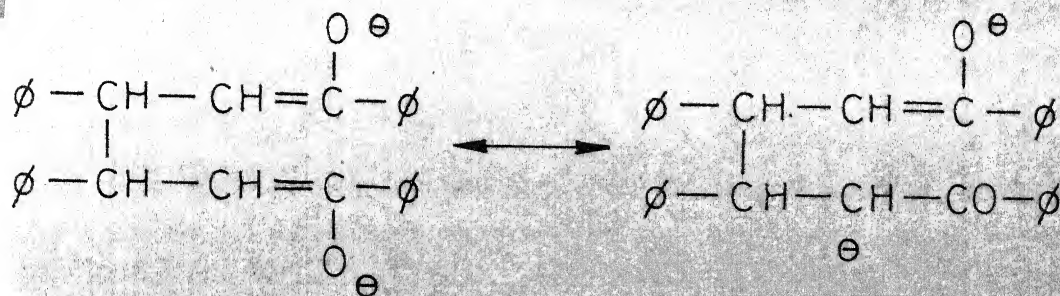
(XIV)

(XV)

 $\text{H}^\oplus$ 

(XVI)

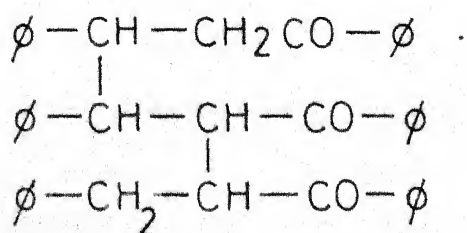
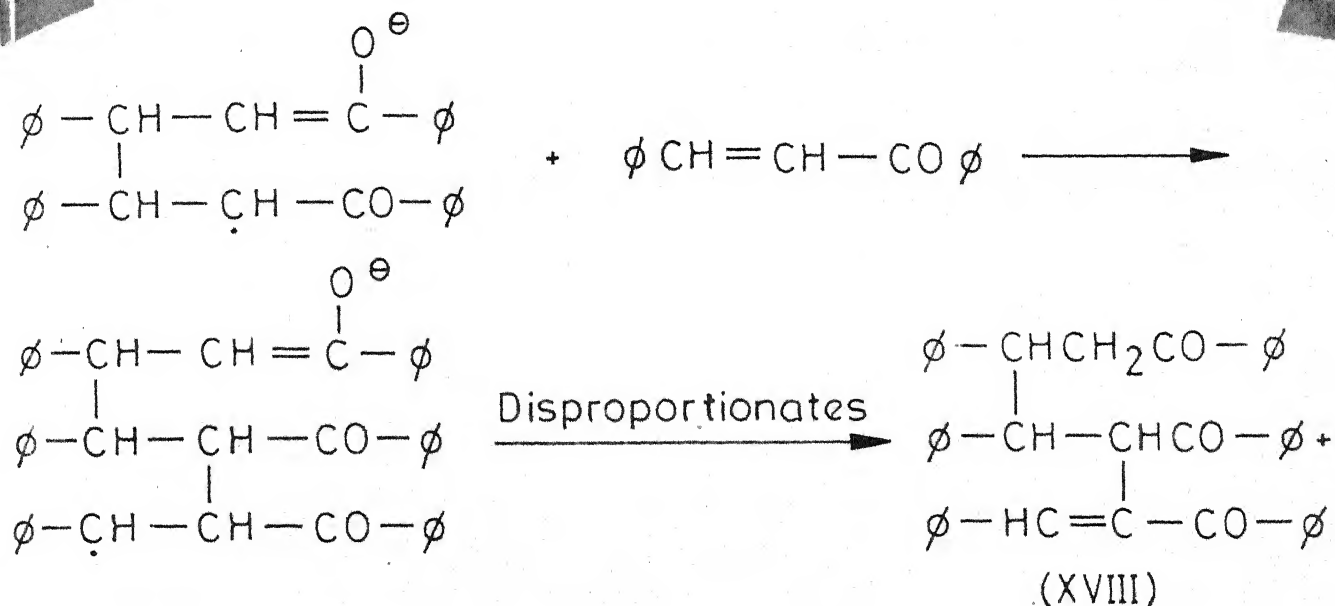
in the absence of carbon dioxide, the chalcone dianion furnishes the polymer<sup>9</sup> (XVII). The polymer must have been produced by a series of Michael type addition of the dianion intermediate



(XVII)



The formation of the unsaturated trimer, (XVIII), in the polarographic reduction of chalcone (in the absence of carbon dioxide) has been assumed<sup>9</sup> to involve the following intermediates:



(Not isolated)

The ease of polarographic reduction is dependent upon the nature of substituents.<sup>4,15</sup> Thus chalcones containing a hydroxyl<sup>4</sup> or methoxy<sup>4,15</sup> function (in conjugation with the carbonyl group<sup>4</sup>) are less prone to reduction as compared to chalcone bearing an acetoxy function. This effect is less pronounced in acid medium than in neutral medium.<sup>16</sup>

### Polarographic Reduction of Chalcone Analogues:

The polarographic reduction of ferrocenyl<sup>7,20</sup> and heterocyclic analogues of chalcone (viz., pyrrolyl, furanyl, thienyl and pyridyl) are reported in the literature. The polarographic reduction of furan chalcone is reported to take place via radical anion formation.<sup>23,24</sup> The behaviour of pyridyl<sup>21,22</sup> analogues of chalcone in respect of polarographic reduction is similar to that of chalcone.<sup>25</sup> In alkaline medium other reactions<sup>26</sup> manifest themselves, viz., the hydration of the double bond, followed by cyclization to chromanones ( $p_H \sim 12.5$ ), which are in turn polarographically reduced further.

The polarographic reduction behaviour of chalcone has been studied<sup>27</sup> and compared with its acetylenic analogue, viz., 1,3-diphenyl-1-propyn-3-one.

### Polarographic Analysis of 2'-hydroxychalcone-flavanone Mixture:

In weakly acidic or neutral medium chalcone shows two polarographic reduction potentials,<sup>3</sup> while flavanone has only one. Based on this property it is possible to determine 2'-hydroxychalcone in the presence of its isomer, flavanone.<sup>3</sup> Polarographic method could also be used to monitor the rate of formation of chalcone from its components.<sup>3</sup>

### Polarographic Conversion of 2'-hydroxychalcone to Chromanone:

A polarographic study of the transformation of ortho-hydroxychalcone to chromanones has been reported.<sup>28,29</sup> The

percentage of hydroxychalcone at equilibrium is independent<sup>29</sup> of pH (range 5-9), however, with pH greater than 9, the equilibrium is displaced in favour of chalcone, attended with immediate decomposition.

#### Polarographic Conversion of Chalcone to Chalcone Hydrazone:

A polarographic study has been reported in respect of the reaction of chalcone with phenylhydrazine.<sup>30</sup> Conclusion has been drawn<sup>31</sup> that the first step, is the reaction on mercury cathode of the carbonyl group of the chalcone.

#### Polarographic Behaviour of Pyridine Analogue of Chalcone Oxime:

The pyridyl analogue of chalcone oxime,<sup>32</sup>  $R_1C(NO\dot{H})-CH=CH-R_2$  ( $R_1 = R_2 = 3$ -pyridyl) is reported to undergo protonation and polarographic reduction at the oximo group, and then at the olefinic linkage.

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P A R T - I I I



CHAPTER - 10

## PROPERTIES OF CHALCONES AND THEIR HETEROCYCLIC ANALOGUES

Viscosity.....	211
Rate of Crystallization.....	212
Adsorption Characteristics.....	212
Quenching of Fluorescence.....	212
Eutectic and Molecular Compound Formation.....	213
Molecular Refraction.....	213
Polymorphism.....	214
Basicity.....	216
Hydrogen Bonding.....	216
Electronic Effects.....	217
Halochromism.....	218
References.....	219

Viscosity:

The specific viscosity of chalcone in benzene and carbon tetrachloride is reported<sup>1</sup> to be higher compared to dihydrochalcone. At higher temperature (Ca. 60°) the decrease in specific viscosity is slightly less in benzene than in carbon tetrachloride.

### Rate of Crystallization:

The rate of crystallization has been taken as a criterion of purity of chalcone.<sup>2</sup> The maximum rate of crystallization (m.r.c.), expressed as mm/minute has been reported<sup>2</sup> for the following chalcones:

<u>Compound</u>	<u>M.P. (°C)</u>	<u>m.r.c. (temp.)</u>
Chalcone	54.7	5.21 (30°)
p'-Ethylchalcone	61.0	1.15 (25°)
p'-Propylchalcone	45.7	3.62 (25°)

### Adsorption Characteristics:

Chalcone undergo polarization and color change when these are adsorbed on surface active materials, like silica gel, acid washed alumina and Brockmann's alumina. These color changes along with the ease of their elution (by methanol) from these adsorbents<sup>2</sup> are described<sup>3</sup> in the literature.

A study in respect of distribution of para N,N-dimethyl-chalcone (DMC) in artificial lipid membrane has been reported.<sup>4</sup> DMC molecules have been found<sup>4</sup> to concentrate in the polar regions - near the surface of the lipid membrane.

### Quenching of Fluorescence:

Hesperatin chalcone, in contrast to hesperidin or eriodictin, is able to quench the fluorescence of chrysene solution (in

acetone) and this has been attributed<sup>5</sup> to its ability to form a non-fluorescent complex.

#### Eutectic and Molecular Compound Formation:

Chalcone forms an eutectic<sup>6</sup> with picric acid and with trichloroacetic acid. A detailed study is reported<sup>7</sup> in respect of eutectic composition of the ternary system, viz., chalcone- $\beta$ -naphthol picric acid (cf. Table 1).

Table 1  
Eutectic Composition

Temp. °C	Chalcone	$\beta$ -naphthol	Picric acid
70	51.5	43.0	5.5
84	58.5	16.0	25.5
103	7.5	7.5	8.5

The molecular compounds formed between chalcone (and 3,4-methylenedioxychalcone) and isomeric nitrophenols (and o-nitrotoluene) have been studied.<sup>8,9</sup>

#### Molecular Refraction:

Refractometric studies of chalcones and some of its derivatives are reported<sup>10,11</sup> in the literature.

Polymorphism:

The phenomenon of polymorphism is well known in the case of chalcones. The work reported on the subject is summarized in Table 2.

Table 2  
Polymorphic Forms of Chalcones

Compound	Melting point (°C) of poly- morphic forms	Remarks	Ref.
Chalcone*	59,57,49,48, 30,—	Several polymorphic forms are known. No difference is observed in the infrared spectrum of the polymorphs, recorded in the range 2222-1220 $\text{cm}^{-1}$ . The dipole moment data (calcd.) for some polymorphic forms are given.	12,13,15, 16,22.
<u>m</u> -Methyl- chalcone	68,67,66,53		14
<u>m'</u> -Methyl- chalcone	61,51		14
<u>p</u> -Methyl- chalcone	99,96.5,90	Exists in three polymorphic forms	24,27
<u>p'</u> -Methyl- chalcone	74.5,56.5, 55.5,54.5, 45.5,48 and 44.5		26
<u>o</u> -Nitro- chalcone	126,123		14
<u>m</u> -Nitro- chalcone	146,145,120		14

<u>m'</u> -Nitro-chalcone	131,110		14
$\alpha$ -Bromo-chalcone	—	Exhibits polymorphism	12
$\beta$ -Hydroxy-chalcone	81,78,73	Exhibits polymorphism	12,28
$\beta$ -Methoxy-chalcone	81,78,65	X-ray powder diffraction, uv and IR spectral data have been recorded	12,17,18
$\beta$ -Ethoxy-chalcone	81,78,75,63,43	Polymorphism is due to the existence of rotational isomers	21,25,28
$\beta$ -Propoxy-chalcone	75,63,59	X-ray powder diffraction and UV studies have been carried out	21
$\beta$ -Methoxy-p-nitro-chalcone	97,90,78-81,66-9,55-8	Polymorphism attributed to rotational isomers u.v. data is reported	20
$\beta$ -Methoxy-p'-nitro-chalcone	121,107,104	Polymorphic forms (107,104*) 19 possess identical x-ray powder diffraction, while the polymorph, m.p. 121° has a different pattern. Results confirmed by u.v. and IR data	
$\beta$ -Methoxy-p'-methoxy-p-nitro-chalcone	132,87,80		22
$\omega$ -Furfuryl-acetophenone	60,56		13

— indicates that polymorphism has been observed, but the melting point of the polymorphs are not available.

\* It is reported<sup>23</sup> to be in a mesophase near its melting point, it exhibits a rapid increase in transmission of the infrared radiation at this stage of phase change.

### Basicity:

The basicity of chalcone has been determined in sulpholane and water. The  $pK_a$  value, -5.55 is reported<sup>6</sup> for chalcone in sulpholane solvent, compared to -5.73 in water.

The basicity of chalcone in acetic acid is reported<sup>29</sup> to be higher than in aqueous solution. The electron donating substituents, viz., hydroxy, methoxy, methyl, increase the basicity, whereas the para substituted halogens decrease it.<sup>29</sup>

The basicity of trans chalcone in concentrated sulphuric acid has been shown<sup>30</sup> to be more than its corresponding cis isomer.

Protolytic equilibrium in respect of substituted chalcones<sup>31,32</sup> and thiophene analogues<sup>33</sup> have been studied in acetic acid-sulphuric acid system. The comparison of relative basicities of these chalcones have been made.<sup>31,33</sup> Correlation has been found between the protonation data and the  $\sigma$ -constants.<sup>31</sup>

Substitution of the phenyl ring of chalcone by either furan<sup>34</sup> or thiophene moiety<sup>35-37</sup> increase the basicity. The effect is reported<sup>34,37</sup> to be pronounced when the heterocyclic moiety is located further away from the carbonyl group. Comparative studies in respect of basicities of heterocyclic chalcone analogues have been published.<sup>38-40</sup>

### Hydrogen Bonding:

The energy of hydrogen bonding involved in phenol and

various chalcones, in carbon tetrachloride has been determined.<sup>41</sup> The thermodynamic data for the (1:1) association of the above system has been reported.<sup>42</sup> The association constants have been shown<sup>43</sup> to be a sensitive measure of the proton-acceptor power of chalcones.<sup>43</sup> ~~than the shifts of the I.R. and N.M.R. absorption bands.~~

Based on uv absorption data, the energy of the hydrogen bond formed between various substituted chalcones and trichloroacetic acid has been found<sup>44,45</sup> to lie in the range 1.79-2.40 kcal/mole. Also, the  $\Delta H$  values,<sup>46</sup> calculated from the equilibrium constants at various temperatures, have been shown to vary from 2-3 kcal/mole.

The hydrogen bonding of 2,3,4,6-tetrachlorophenol with various chalcones have been studied<sup>43</sup> by infrared and N.M.R. spectroscopy.

#### Electronic Effects:

The influence of several functional groups on the activity of methyl group in chalcone has been investigated.<sup>47</sup>

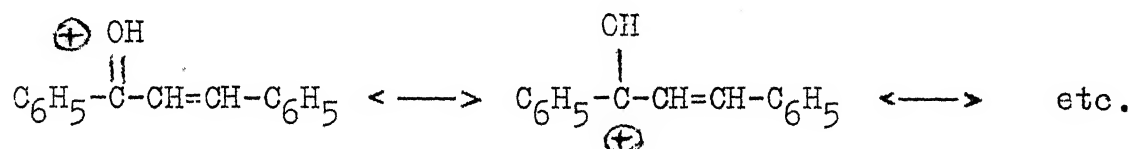
The quantum-chemical interpretation of reactivity of substituted chalcones (benzene and ferrocene type) has been made.<sup>48</sup> The effect of substituents on the  $\pi$ -electron structure and reactivity of monosubstituted trans chalcones has been studied.<sup>49</sup>



The influence of transmission of electronic effects in Z and E isomers of  $\alpha$ -phenyl-4-substituted chalcones has been investigated.<sup>50</sup> Z and E isomers are reported<sup>50</sup> to be insensitive to substituent effects.

#### Halochromism:

The phenomenon of halochromism is reported for substituted chalcones<sup>51-56</sup> and their heterocyclic analogues containing either a furan,<sup>57,58</sup> thiophene,<sup>59,61</sup> selenophene<sup>60</sup> or quinoline<sup>62</sup> nucleus. These chalcones develop halochromic colors when wetted with concentrated sulphuric acid. The deepening in color may be rationalized in terms of the formation of carbonium ions in concentrated sulphuric acid.



Methoxychalcones,<sup>56</sup> for example, also exhibit halochromism with other mineral acids, viz., hydrochloric and phosphoric acids. The color is reported<sup>56</sup> to deepen with increase in the number of methoxy groups.

The influence of various substituents on the halochromy of these compounds in concentrated sulphuric acid is described<sup>51-54</sup> in the literature. In the case of quinoline analogue of chalcone, the halochromic color deepens when the heterocyclic residue is located closer to the carbonyl group.<sup>62</sup>

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CHAPTER - 11

## COMPLEXING ACTION OF CHALCONES AND THEIR DERIVATIVES

Chalcones serve as starting materials for the preparation of ligands suitable for the quantitative precipitation of several metallic ions. This, therefore, forms the basis for their gravimetric estimation. The following two examples<sup>1-4</sup> are illustrative:

2'-Hydroxy-4-methoxy-5'-methyl chalcone oxime<sup>1-3</sup> has been employed for the gravimetric estimation of divalent ions of palladium, copper and nickel either separately or in combination.

2,4,6-Triphenylpyrylium chloride,<sup>4</sup> preparable from chalcone, has been used as a precipitant in the gravimetric estimation of gold and platinum.

A method of separation of palladium (II) from copper (II) involving the use of 2'-hydroxy-5'-methylchalcone oxime (as complexing agent) has been developed.<sup>5</sup> It is based on extraction, with a suitable solvent, of the resulting organo-metallic complex, at a definite pH. The constituents thus separated have been determined spectrophotometrically.<sup>5</sup> 2'-Hydroxy-3'-bromo-4-methoxy-5'-methylchalcone oxime has been successfully employed<sup>6</sup> in place of the aforesaid complexing agent.

A spectrophotometric method of estimating beryllium, using 2'-hydroxychalcone has been described.<sup>7</sup> Hydroxychalcones have been exploited as specific precipitants,<sup>8</sup> (in the



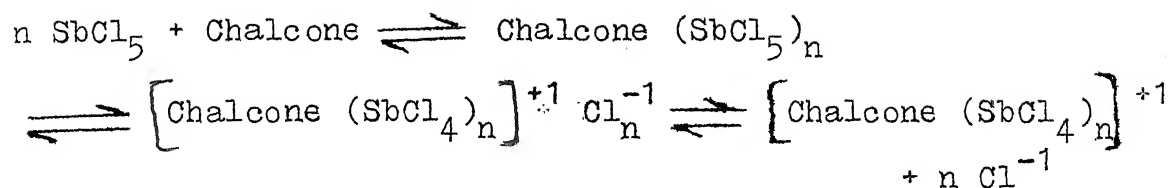
presence of EDTA) for beryllium when present in combination with aluminium. Copper is reported<sup>9</sup> to react with 2'-hydroxychalcone to form a complex which has a 1:2 stoichiometry. On the basis of this reaction, a conductometric method of estimation of copper has been developed.<sup>9</sup> Calcium has been determined<sup>10</sup> by complexometric titration by using chalcone-metanil as indicator.

The 1:1 complexes formed by the interaction of 2,2'-dihydroxychalcone (sodium salt) with the ions of copper (II), nickel (II) and tin (IV) have been studied.<sup>11-14</sup> The formation constants of several 1:1 complexes, derived from the interaction of several metallic ions with 2'-hydroxychalcone<sup>15,16</sup> and 2',4'-dihydroxychalcone,<sup>17</sup> have been determined.

The preparation of complexes derived from the reaction of 2'-hydroxychalcones with tri- and tetracarbonyl of iron, have been reported.<sup>18</sup>

There are several reports<sup>19,22-24,26-31</sup> in the literature about the preparation, spectroscopic and conductometric studies of the intermolecular complexes formed between chalcones and the halides of the following elements. Ti,<sup>19-21</sup> Fe,<sup>26</sup> Zn,<sup>24</sup> La,<sup>23</sup> Ce,<sup>21</sup> Pr,<sup>23</sup> Sm,<sup>23</sup> Eu,<sup>23</sup> B,<sup>24,25</sup> Al,<sup>26</sup> Si,<sup>22</sup> Ge,<sup>22</sup> Sn,<sup>22,26</sup> and Sb.<sup>26-31</sup>

The complexes of chalcones with antimony pentachloride have, however, been studied in detail. Thus, on the basis of conductometric measurements, the existence of the following species have been proposed<sup>27</sup>:



where  $n = 1$  or  $2$ .

There are two factors of paramount importance in respect of conductivity of the above complex,<sup>27</sup> in benzene solution, viz., temperature and the electron donating ability of the substituents in the chalcone component.

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CHAPTER - 12

## COLOUR REACTIONS, DETECTION AND ESTIMATION OF CHALCONES

## Colour Reactions

With Sulphuric Acid-Nitric Acid.....	
Sulphuric Acid-Acetic Anhydride.....	
Sodium Borohydride-Hydrochloric Acid.....	
Wilson Boric Acid Test.....	
Antimony Pentachloride Test.....	
Detection and Estimation of Chalcone(s).....	
References.....	

Colour ReactionsWith Sulphuric Acid-Nitric Acid<sup>1</sup>:

When the intensely coloured solution of chalcone in concentrated sulphuric acid is treated with a little of concentrated nitric acid, characteristic colour changes occur. This is typified by the following examples:

Chalcone :	Orange → yellow
4-Methoxychalcone :	Orange red → yellow
Cinnamylideneacetophenone :	Cherry red → dark yellow.

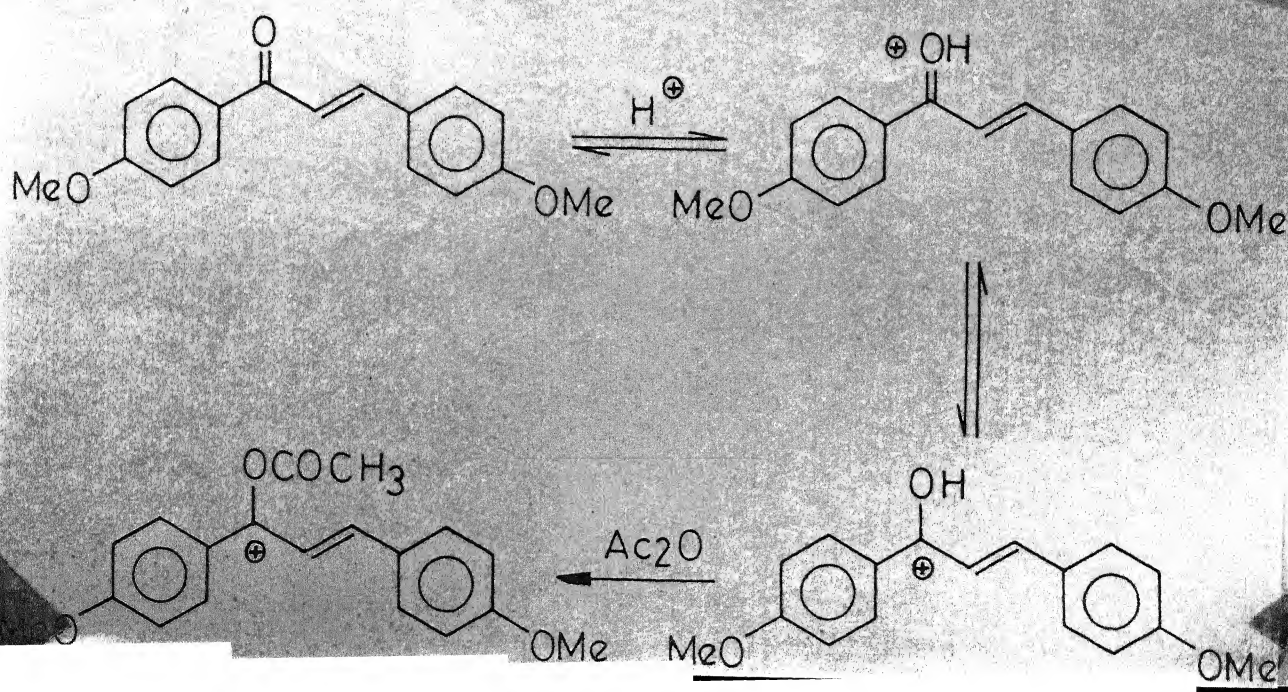
This change involve nitration of chalcone, rather than oxidation, and the resulting nitrochalcones exhibit weaker halochromy as compared to unsubstituted chalcone.

With Sulphuric Acid-Acetic Anhydride:

The differing halochromic effects produced with concentrated sulphuric acid serve to characterize chalcones. Carbonium ions are believed to be formed as intermediates in this reaction. A large bathochromic shift in the visible colour appears if acetic anhydride is incorporated with sulphuric acid. Thus, on treatment with a 200:1 (V/V) mixture of acetic anhydride-sulphuric acid, chalcones gave orange to purple colours<sup>2</sup>:

3,4,4'-Trihydroxychalcone	. . . .	Orange
3,4'-Dihydroxy-4-methoxychalcone	. . . .	Cerise
3,4,4'-Tribenzyloxychalcone	. . . .	Red
3,4,4'-Trimethoxychalcone	. . . .	Purple

The bathochromic shift arising due to the addition of acetic anhydride to the chalcones (in concentrated sulphuric acid) has been rationalized<sup>3</sup> in terms of stability conferred on the carbonium ion by acetylation with acetic anhydride. This is illustrated (vide infra) with reference to 4,4'-dimethoxy-



With Sodium Borohydride and Hydrochloric Acid:

Transient colours are developed when chalcones, after reduction with sodium borohydride, are treated with concentrated hydrochloric acid. This colour test can, therefore, be utilized for their identification. Table 1 lists the absorption maxima recorded after the chalcones were subjected to the aforesaid test<sup>3</sup>:

Table 1

<u>Chalcone</u>	<u><math>\lambda_{\text{max}}</math> (nm)</u>
4'-Hydroxychalcone	480-485
4-Methoxychalcone	550
4,4'-Dimethoxychalcone	565
2'-Hydroxy-4,4',6-trimethoxychalcone	540
2'-Hydroxy-3,4,4',6'-tetramethoxychalcone	560
4-Dimethylaminochalcone	495
2'-Hydroxy-4,4-dimethyl <sup>a</sup> aminochalcone	550

Wilson's Boric Acid Test:

The test consists in reacting chalcones with boric acid-citric acid mixture in acetone solution, when a coloration is developed. Partially methylated hesperetin chalcone is reported<sup>4</sup> to give a positive test. The boric acid-citric acid test is very specific for 5-hydroxy and methoxychalcones.<sup>5</sup>



### Antimony Pentachloride Test<sup>6</sup>:

Antimony pentachloride in carbon tetrachloride gives with various chalcones, intense red or violet precipitates, which are characteristically different from the precipitates from flavones, flavanones and flavanols, which are yellow or orange. A positive test is obtained with the chalcones listed in Table 2.<sup>6</sup>

Table 2

Colours obtained with various chalcones in the  $\text{SbCl}_5$  test

<u>Chalcone</u>	<u>Colour</u>
2-Hydroxy-2-methoxychalcone	Blood red
2-Hydroxy-4,5-dimethoxychalcone	Red
2-Hydroxy-4,4'-dimethoxychalcone	Red
2-Hydroxy-4',4,5-trimethoxychalcone	Blood red
2-Hydroxy-3,4,4'-trimethoxychalcone	Red
2-Hydroxy-3,4,5-trimethoxychalcone	Red
2-Hydroxy-4,5-dimethoxy-3',4'-methylenedioxychalcone	Cherry red
2-Hydroxy-3,4,4',6-tetramethoxychalcone	Red
2-Hydroxy-3,3',4,4',5-pentamethoxychalcone	Cherry red
2-Hydroxy-3,4,4',5-tetramethoxychalcone	Brick red
2,2'-Dihydroxy-3',4',5,6,6'-pentamethoxychalcone	Violet red
3,6-Dihydroxy-2,4,4'-trimethoxychalcone	Violet red
4-Methoxychalcone	Red
3',4'-Dimethoxychalcone	Cherry red

Table 2 (continued)

3',4'-Methylenedioxychalcone	Violet red
2',4,4'-Trimethoxychalcone	Red
2,4,4',6-Tetramethoxychalcone	Dark red
2,3,4,4',5-Pentamethoxychalcone	Red
2,3,4-Trimethoxy-3',4'-methylenedioxychalcone	Cherry red

Antimony pentachloride reaction is an extremely sensitive test. For example, 2-hydroxy-3,4,4'-trimethoxychalcone, can be detected in as low a concentration as 1 part per million.

The colour reactions <sup>of</sup> by chalcones with various reagents are reported in the literature.<sup>7</sup>

#### Detection and Estimation of Chalcone(s):

A spot test for chalcone has been developed.<sup>8</sup> It is based on the pyrolytic oxidative cleavage of chalcone by lead dioxide. Benzaldehyde - the product of reaction - is identified (identification limit : 50%) by the appearance of yellow colour with thiobarbituric acid and phosphoric acid.

Chalcone may also be characterized by chromatography of its 2,4-dinitrophenylhydrazone<sup>9</sup> ( $R_f$ , 0.54) on paper, impregnated with diethyl ether - N,N-dimethylformamide-tetrahydrofuran (85 : 15 : 4; V/V).

A scheme is reported for the qualitative identification of two chalcones,<sup>10</sup> e.g., methylchalcone and tetramethoxy-eriodictyolchalcone, following separation by paper chromatography.

The chalcone (identification limit : 5%) on the chromatogram is revealed as a yellow fluorescent spot, after spraying it with isonicotinic acid hydrazide reagent.

Methods for the separation and subsequent identification of chalcone in lemon oil are described in the literature.<sup>11,12</sup> According to one method,<sup>12</sup> TLC has been employed for the purpose, using ethylacetate-hexane (3:2) as the elutotropic solvent. Various chromogenic reagents are available for identification, which include concentrated hydrochloric acid, antimony trichloride (chloroform solution), 2,4-dinitrophenylhydrazine and nicotinic acid hydrazide.

For quantitative estimation<sup>12</sup> of chalcones in lemon oil, the latter is reacted with nicotinic acid hydrazide and after 2 hours, absorbance of the reaction mixture is recorded at around 404 nm, by means of a spectrophotometer. Alternatively, chalcones may be determined gravimetrically<sup>13</sup> by utilizing ~~its~~<sup>their</sup> reaction with 2,4-dinitrophenylhydrazine. A spectrophotometric method for the determination of 2',4'-dihydroxychalcone and 7-hydroxyflavanone has been developed.<sup>14</sup> For this purpose the absorbance of the alcoholic solution of the mixture is measured at 320 nm.

p-substituted benzohydrazides ( $X-C_6H_4CONHNH_2$ ;  $X = NO_2$ , Br or I) have been recommended<sup>15-17</sup> as reagents for the identification of chalcone. The melting points of the hydrazones are claimed<sup>17</sup> to differ sufficiently to make identification possible, without the determination of mixed melting points:

<u>Compound</u>	<u>m.p.</u>
Chalcone-p-nitrobenzohydrazone	232°
Chalcone-p-bromobenzohydrazone	170°
Chalcone-p-iodobenzohydrazone	182°

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CHAPTER - 13.1

## STEREOISOMETRISM IN CHALCONES AND THEIR DERIVATIVES

Introduction.....	237
<u>Cis-trans</u> Isomerism.....	238
Mechanism of Acid Catalysed Isomerization	
Mechanism (A).....	239
Mechanism (B).....	240
Tautomerism in $\alpha$ -Hydroxychalcone.....	242
Stereoisomerism of Chalcone Semicarbazones.....	242
Thiosemicarbazones.....	243
References.....	243

Introduction:

The stereoisomers of chalcone have been examined<sup>1</sup> in respect of their physical (colour, crystallography and transmutation) and chemical properties. It exists in several forms, presumably arising due to polymorphism and/or stereoisomerism.<sup>2</sup> The introduction of methoxy or ethoxy group in the  $\beta$ -position of chalcone molecule exert different effects on isomerism. Conclusion has been drawn<sup>2</sup> that mass of the groups about the olefinic system and particularly their spatial effects, determine the number of isomers obtainable in a given case.

The relationship between polymorphism and stereoisomerism in respect of substituted chalcones has been discussed.<sup>3</sup>

The  $\alpha$ -bromo- $\beta$ -methoxychalcone<sup>4</sup> exists in two stereoisomeric forms. The most stable form has the highest melting point and is easier to isolate.<sup>4</sup> The stereoisomers have been interconverted into each other under appropriate experimental conditions.<sup>6</sup>

$\alpha$ -Bromo- $\beta$ -methoxy (and  $\beta$ -ethoxy) chalcones also exist in several crystalline forms with different melting points.<sup>5</sup> However, their homologue, viz.,  $\alpha$ -bromo- $\beta$ -propoxychalcone exists only in one form.

#### Cis-trans Isomerism:

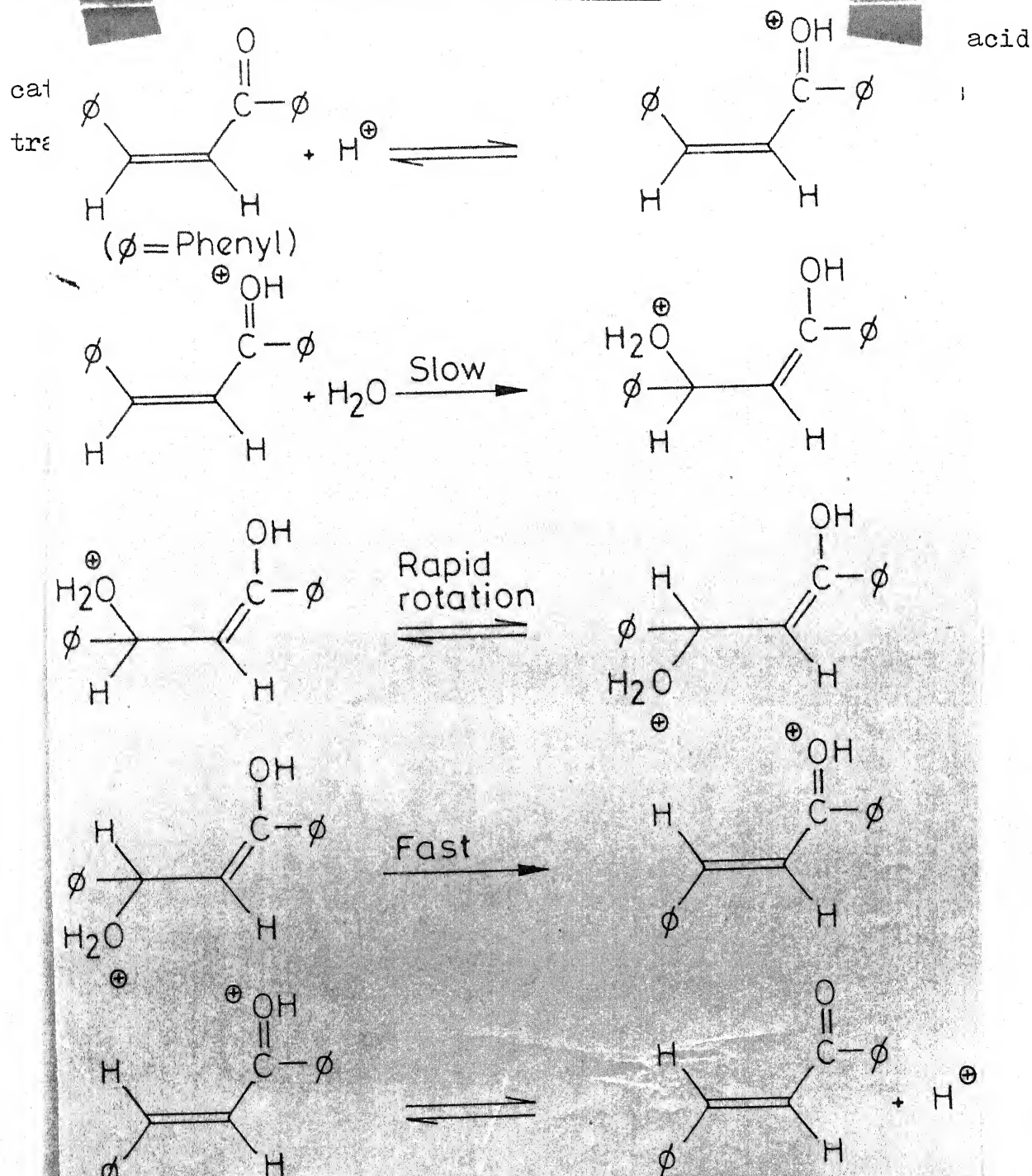
There are various reports<sup>7-12</sup> about the existence of geometrical isomers of chalcones. The well-known examples are: chalcone,<sup>7-9</sup>  $\alpha$ -phenylchalcone,<sup>11,20</sup>  $\beta$ -tolylchalcone<sup>10</sup> and  $\alpha$ -phenyl-nitrochalcone.<sup>12</sup>

The partial transformation of trans-chalcones into stereoisomeric pairs have been accomplished either by irradiation of their solution (in pentane or iso-octane) to sunlight or by treatment with anhydrous aluminium chloride.<sup>13,23</sup> The percentage of cis- and trans-isomers formed on irradiation is reported<sup>14</sup> to vary greatly from one chalcone to another. The reverse conversion from cis to its stereoisomeric pair can be effected thermally<sup>7</sup> or by acid catalysis.<sup>8</sup>

The ultraviolet spectra of cis-trans isomers of chalcones have been studied.<sup>15-17</sup> Their spectra are quite different with a large extinction coefficient for the more stable trans isomer.

In the acid catalysed isomerisation of cis to trans chalcone either of the following mechanisms (A and B) are involved:

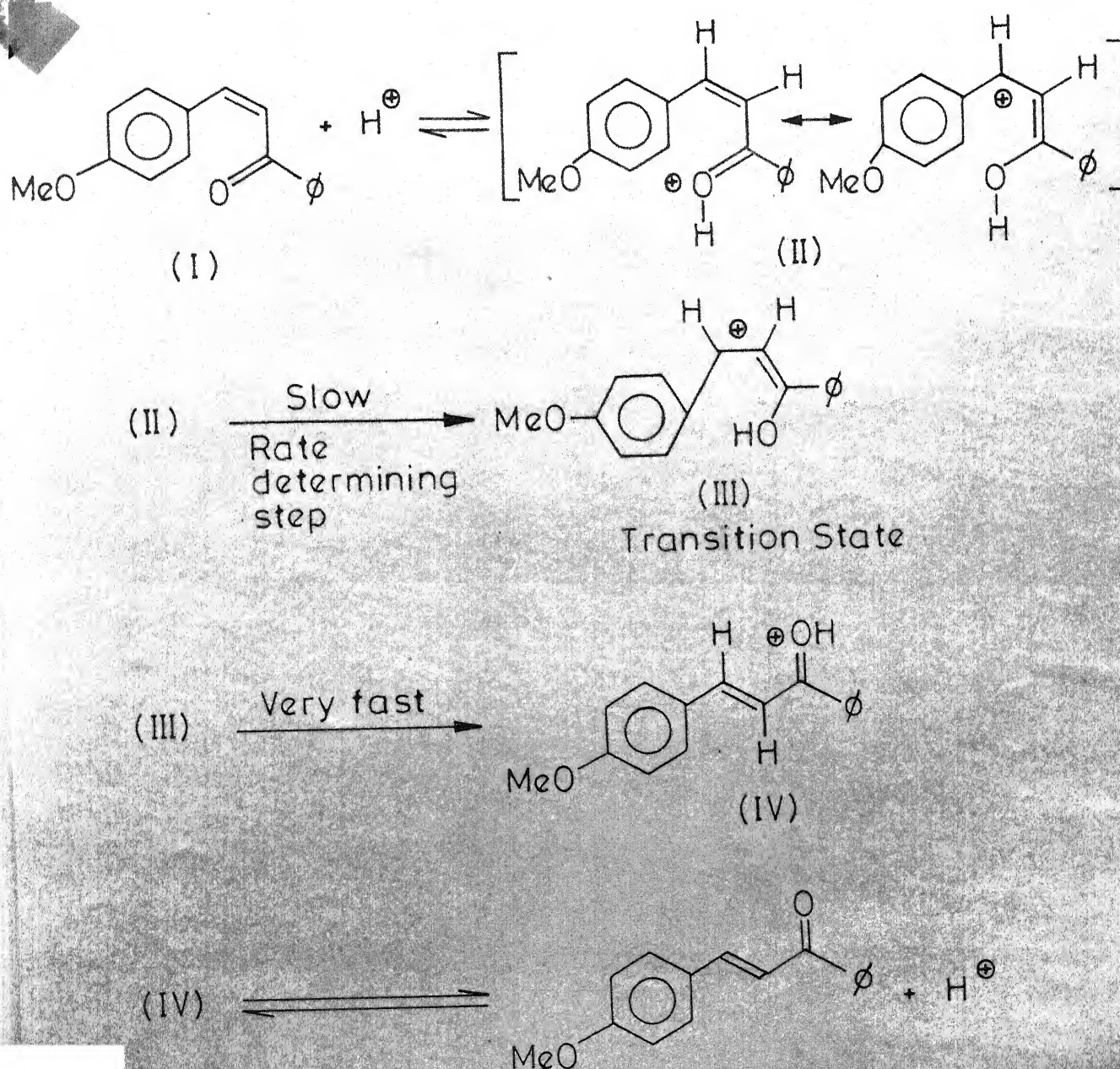
Mechanism of Acid Catalysed Isomerization:





The rate controlling process is the addition of water to the conjugate acid (oxonium salt) of cis-chalcone. Following this slow step, rapid rotation about the C-C bond occurs, and this is followed by dehydration. The mechanism outlined above finds support in the deuterium isotope studies<sup>9</sup> on this transformation.

Mechanism B (Carbonium ion mechanism):



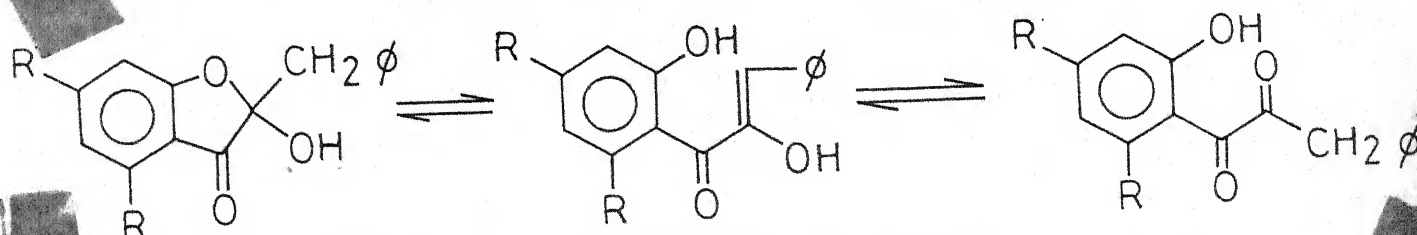
The salt of the ketone (II), is resonance stabilized and undergoes rotation about  $C_{\alpha} - C_{\beta}$  bond without the addition of water.

The isomerization may change from mechanism (A) to mechanism (B) depending upon the substituents present in the chalcone molecule, as well as on the conditions of experiment.<sup>19</sup> Thus, introduction of a methoxy group in the 2-, 4- and 6-positions will exert a very great influence on the stability of the postulated benzylic carbonium ion (II) and thus favours isomerisation by the latter mechanism. Also, by reducing the activity of water the rate of isomerisation by mechanism (A) may be reduced and thus allow mechanism (B) to become competitive. Besides, the introduction of ortho substituents will provide some steric interference to the addition of water at the  $\beta$ -carbon and likewise allow the carbonium ion mechanism to become competitive. The isomerisation of cis-chalcone into trans-chalcone occurs in 78% sulphuric acid via mechanism (A), while mechanism (B) operates when the reaction is carried out in a sufficiently concentrated sulphuric acid (96%).

The mechanism and kinetics of cis-trans photoisomerization of chalcone has been reported.<sup>21</sup> The reaction has been described<sup>21</sup> to take place by a triplet mechanism, wherein a direct conversion of the twisted state of one isomer to the ground state of the other takes place.

### Tautomerism in $\alpha$ -Hydroxychalcone:

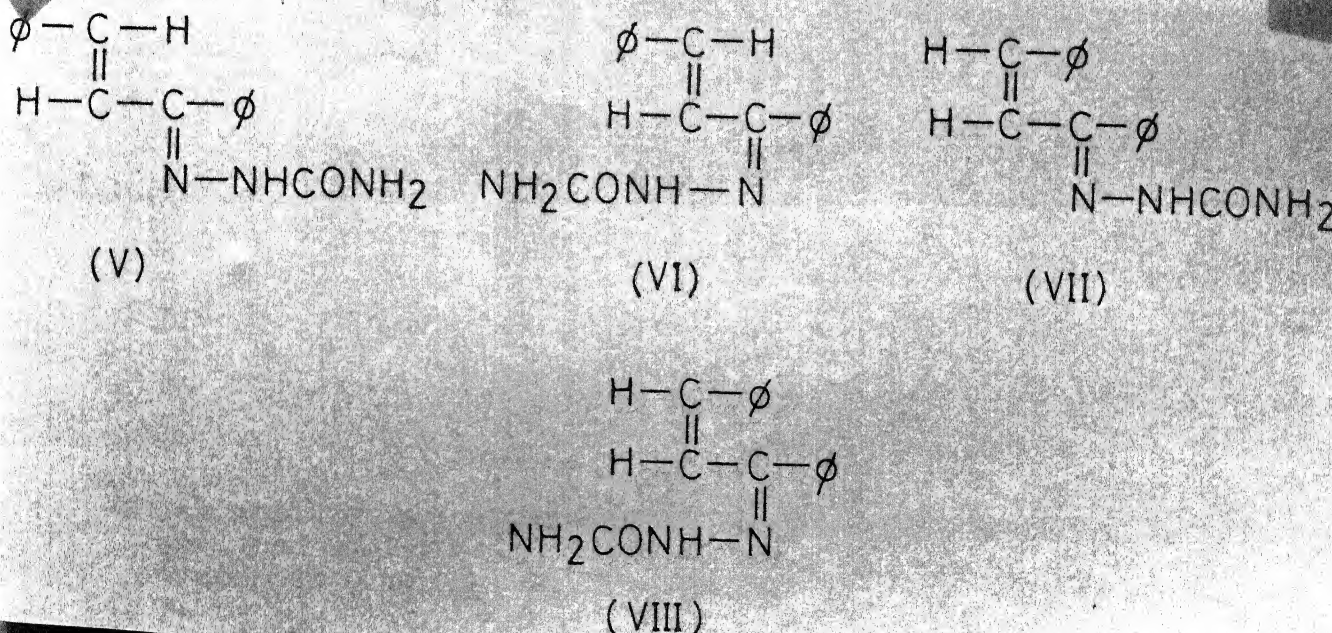
$\alpha$ -Hydroxychalcone is reported<sup>22</sup> to exhibit tautomerism. It exists in equilibrium with corresponding Coumaran-3-one and the diketone,<sup>22</sup> thus:



### Stereoisomerism of Chalcone Semicarbazones

#### Chalcone Semicarbazones:

Chalcone react with semicarbazide in acetic acid medium to give three isomeric semicarbazones<sup>24</sup> ( $\alpha$ ,  $\beta$  and  $\gamma$ -). According to Hantzsch-Werner hypothesis four semicarbazones (V-VIII) are



semicarbazones are possible. Similar behaviour is exhibited by the isomers of chalcone phenyl semicarbazone.<sup>25</sup>

### Chalcone Thiosemicarbazones:

Thiosemicarbazone of substituted chalcones (with substitution in both the aromatic rings) are described in literature.<sup>26</sup> The thiosemicarbazone of chalcone and 2-nitrochalcone are reported<sup>27</sup> to exhibit prototropic and thermochromic properties.

Chalcone semicarbazone and thiosemicarbazone formed under acid catalysis, are reported<sup>28</sup> to have trans and anti configuration, with respect to the olefinic hydrogens. On the other hand, cis and syn products are formed in the base catalysed reaction.

Chalcone semicarbazone derivatives are claimed<sup>29,30</sup> to be useful for characterisation of chalcone. For the preparation of these derivatives the following two reagents have been recommended, viz., 2,4-dinitrophenyl semicarbazide<sup>29</sup> and  $\alpha$ -naphthyl-semicarbazide.<sup>30</sup> The reagents can readily be prepared by the interaction of hydrazine hydrate with the appropriately substituted urea in alcoholic solution.

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CHAPTER - 13.2

## STEREOCHEMISTRY OF CHALCONES AND CHALCONE ANALOGUES

Introduction.....	246
X-ray Crystallographic Studies on Unsubstituted Chalcone and its	247
Polymorphic Forms.....	247
4'-Bromochalcone.....	248
4-Methoxychalcone.....	248
4,4'-Dimethylchalcone.....	248
Halonitrochalcones.....	249
Dipole Moment Studies on Chalcone and its Polymorphs.....	249
Bromochalcones.....	250
Substitution Effects on Dipole Moment of Chalcones and Their	
Heterocyclic Analogues.....	250
<u>Erythro</u> Chalcone Dihalides.....	252
Chalcone Epoxides.....	252
Huckel Molecular Orbital Calculations.....	253
References.....	256

Introduction:

The conformational features of several chalcones have been arrived at by taking recourse to physical methods. The experimental methods for such investigations include, for example, X-ray crystallography,<sup>1-8</sup> dipole moment determination,<sup>9-29</sup>

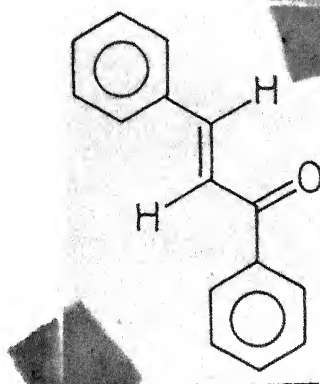


infrared spectroscopy,<sup>27</sup> nuclear magnetic resonance spectroscopy etc. Only the former two methods are detailed in this chapter.

### X-ray Crystallographic Studies on Unsubstituted

#### Chalcone:

Crystal and molecular structure studies based on X-ray crystallographic data are reported<sup>1</sup> for unsubstituted chalcone. It consists of two essentially planar units, which are linked by a non-planar cisoid 1,3-enone bridge twisted about the C-C bond by  $16.9^\circ$ . The assignment of the cisoid conformation



to chalcone finds additional support by the measurement of its molar Kerr constant.<sup>2</sup>

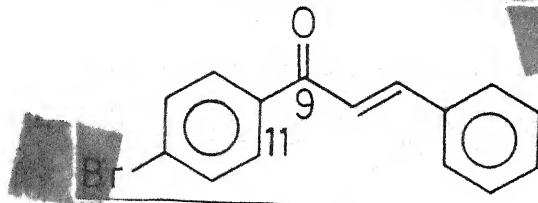
#### Polymorphic Forms of Chalcone:

The conformational details about the polymorphic form of chalcone (m.p.  $56^\circ$ ) have been worked out<sup>3</sup> and compared with other polymorphic form (m.p.  $59^\circ$ ).



4'-Bromochalcone:

4'-Bromochalcone possesses a cisoid conformation,



and there exists a large bond twist ( $26^\circ$ ) about  $C_{(9)} - C_{(11)}$  and the two phenyl rings are situated at an angle of  $50^\circ$  with respect to each other.<sup>4</sup>

4-Methoxychalcone:

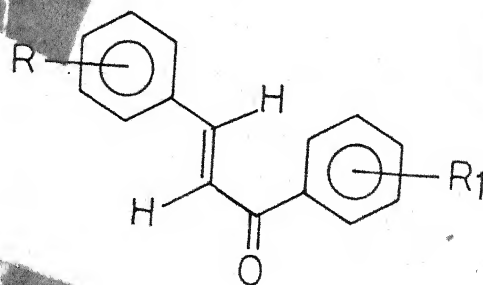
X-ray crystallographic studies<sup>5</sup> in respect of 4-methoxychalcone indicate that the molecule consists of three planar units, viz., methoxyphenyl, enone and phenyl, and the angle between the planar units being  $4.5^\circ$  and  $11.5^\circ$ . A theoretical discussion has been published<sup>6</sup> concerning the conformation of 4 and 4'-substituted chalcones.

4,4'-Dimethylchalcone:

X-ray studies carried on 4,4'-dimethylchalcone<sup>7</sup> reveal that the angle between the planes of the two phenyl rings is  $48.6^\circ$ , which represents a considerable deviation from planarity. This molecular conformation, it is claimed,<sup>7</sup> controls the formation of optically active dibromides in the bromination of a single crystal of 4,4'-dimethylchalcone.

### Halonitrochalcones:

Transoid conformations are reported<sup>8</sup> to exist in the case of 3-chloro-, 3-bromo- and 4-bromo-2'-nitrochalcones.



(Transoid)

### Dipole Moment Studies on

### Chalcones:

Dipole moments of a large number of chalcones<sup>9-11</sup> and their heterocyclic analogues<sup>12-18</sup> have been determined (cf. Table 1). These data have provided useful information regarding the stereochemistry of these molecules. From dipole moment measurement on chalcone for example, it has been established<sup>19</sup> that the double bond has a trans configuration, and the carbonyl group has a S-cis conformation with respect to the adjoining carbon-carbon double bond.

### Polymorphic Forms of Chalcone:

It has been reported<sup>20</sup> that the three polymorphic forms of chalcone (m.p. 59°, 57° and 49° respectively) have the same dipole moment.

### Bromochalcones:

Dipole moment determination of various bromochalcones,<sup>9</sup> viz., 4'-bromochalcone, 4,4'-dibromochalcone,  $\alpha$ ,  $\beta$ -dibromochalcone,  $\alpha$ - and  $\beta$ -bromochalcones have been helpful in deciding whether the polar substituents are on the same or opposite sides of double bond of the chalcone molecule.

### Substitution Effects on Dipole Moment of Chalcones and Their Heterocyclic Analogues:

The effect of substituents on dipole moment of chalcone has been studied.<sup>21</sup> Based on the dipole moment data, the electron transfer through the carbonyl group of 4- and 4'-substituted hydroxychalcones has been determined.<sup>22</sup> With chalcone and 4-substituted chalcones (viz., chloro-, bromo-, nitro- and methoxy) there is no interaction with the  $\pi$ -electron system of the phenyl ring (bearing the substituent) with the carbonyl group. In the case of 4,4-dimethylamino-chalcone, however, there seems to be a direct polar conjugation between the carbonyl function and the dimethylamino group.

Enough data are available on the dipole moment of 4- and 4'-monosubstituted chalcone,<sup>13</sup> furan,<sup>12,16,23,24</sup> thiophene,<sup>12,25</sup> nitrothiophene,<sup>26</sup> selenophene,<sup>12,15</sup> pyrrole<sup>14</sup> and pyridine<sup>23</sup> analogues of chalcone. The stereochemical implications of these data are summarized below:

Polarization caused by a heterocyclic ring is greater than that of phenyl and that the observed dipole moment is generally greater than the calculated value. Similar type of difference have been observed in respect of 4- and 4'-mono-substituted chalcones, and have been ascribed<sup>13</sup> to the conjugation of the molecule.

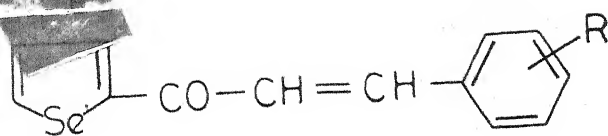
The following conclusions<sup>14</sup> have been drawn in respect of pyrrole analogues of chalcone:

(a) All these compounds exist in trans form.

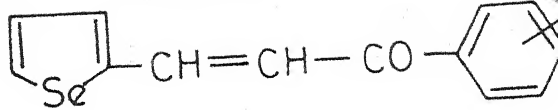
(b) The carbonyl and the vinyl groups assume a S-cis conformation.

(c) The S-cis conformation can exist in two rotational isomers, viz., syn and anti. In the former the NH of the pyrrole and the carbonyl group lie on the same side of the molecule, while in the latter case, these lie on the opposite sides. The syn-configuration predominates owing to the stability arising due to the weak hydrogen bonding between the NH of pyrrole ring and the adjacent carbonyl group. In some of these compounds, however, the anti configuration is preferred, for example, 1-(2-pyrrolyl)-3-arylprop-3-ones and 1-(N-methyl-2-pyrrolyl)-3-phenyl-1-one. The syn-anti conformation is, however, preferred in the case of 1,3-di(2-pyrrolyl) propenone.<sup>14</sup>

The selenophene analogues of chalcone of the type I and II are reported<sup>15</sup> to exist as mixtures of equal amounts of syn-S-cis and anti-S-cis conformers.



(I)



(II)

Similar work is reported in respect of the substituted chalcones of the furan<sup>16,23,24</sup> series. The pyridine analogue, however, is reported<sup>23</sup> to exist in a transoid conformation.

Dipole moment data have been used<sup>10</sup> to establish the configuration of the  $\alpha$ -substituted, viz.,  $\alpha$ -(phenylthio)- and  $\alpha$ -(phenylsulphonyl)-chalcones. Herein the benzoyl group is cis to the phenyl and trans to the hydrogen atom.

#### Erythro-Chalcone Dihalides:

The infrared carbonyl absorption data for erythro chalcone dihalides have been used<sup>27</sup> for calculating the dipole moment of these compounds.

#### Chalcone Epoxides:

The dipole moment data of chalcone epoxides are available in the literature.<sup>28,29</sup> These compounds are reported<sup>28</sup> to exist in gauche conformation. The oxides of the thiophene chalcone analogues exist in S-cis and S-trans conformations,<sup>30</sup> these differing in the mutual orientation of oxirane ring and carbonyl group.

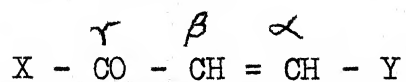
Huckel Molecular Orbital Calculations:

Based on the Huckel molecular orbital calculations, the trans structure and S-cis stereochemistry of 2'-hydroxychalcones have been confirmed.<sup>31</sup>

Table 1  
Dipole moment of chalcones

Compound	Dipole moment (D)	Ref.
Chalcone	2.92,2.97,3.03,3.04	9,13,16,32
4'-Chlorochalcone	2.98	13
4'-Bromochalcone	2.93	9
4'-Methoxychalcone	3.36	13
4'-Methylchalcone	3.19	13
4'-Nitrochalcone	4.21	13
4'-Phenylchalcone	3.12	13
4-Fluorochalcone	2.61	13
4-Chlorochalcone	2.54,2.74	13,32
4-Chloro-4'-methoxychalcone	3.62	33
4-Chloro-2',4'-dimethoxychalcone	4.09	33
4-Bromochalcone	2.47	9
4,4'-Dibromochalcone	2.03	9
$\alpha$ -Bromochalcone	3.87	9
$\beta$ -Bromochalcone	3.59	9
4-Methoxychalcone	3.43,3.40	15,32

4,4'-Dimethoxychalcone	3.65	33
2',4,4'-Trimethoxychalcone	4.08	33
4'-Chloro-4-methoxychalcone	4.05	33
4'-Methyl-4-methoxychalcone	3.85	33
4'-Nitro-4-methoxychalcone	5.54	33
4'-Phenyl-4-methoxychalcone	3.83	33
4'-Chloro-2,4-dimethoxychalcone	4.85	33
2,4,4'-Trimethoxychalcone	4.31	33
4'-Methyl-2,4-dimethoxychalcone	4.29	33
4'-Nitro-2,4-dimethoxychalcone	7.04	33
4'-Phenyl-2,4-dimethoxychalcone	4.40	33
4-Methylchalcone	3.26	13
4'-Methoxy-4-methylchalcone	3.88	33
2',4'-Dimethoxy-4-methylchalcone	4.24	33
4-Nitrochalcone	3.6,3.92	13,32
4'-Methoxy-4-nitrochalcone	4.61	33
4,4-Dimethylaminochalcone	4.88	13
4-Phenylchalcone	3.03	13
4'-Methoxy-4-phenylchalcone	3.65	33
2',4'-Dimethoxy-4-phenylchalcone	4.32	33



$\gamma$ -Keto- $\gamma$ (2-furanyl)- $\alpha$ -phenyl-1-propene	3.19	16
$\gamma$ -Keto- $\gamma$ (5-nitro-2-furanyl)- $\alpha$ -phenyl-1-propene	2.96	16
$\gamma$ -Keto- $\gamma$ (2-furanyl)- $\alpha$ -(4-methoxyphenyl)-1-propene	3.59	16
$\gamma$ -Keto- $\gamma$ (5-nitro-2-furanyl)- $\alpha$ -(4-methoxyphenyl)-1-propene	3.63	16
$\gamma$ -Keto- $\gamma$ (2-furanyl)- $\alpha$ (2,4-dimethoxyphenyl)-1-propene	4.18	16
$\gamma$ -Keto- $\gamma$ (5-nitro-2-furanyl)-(2,4-dimethoxyphenyl) $\alpha$ -1-propene	4.40	16
$\gamma$ -Keto- $\gamma$ (2-furanyl)- $\alpha$ -(4-nitrophenyl)-1-propene	4.43	16
$\gamma$ -Keto- $\gamma$ -phenyl- $\alpha$ (2-furanyl)-1-propene	3.03	16
$\gamma$ -Keto- $\gamma$ (4-methoxyphenyl)- $\alpha$ (2-furanyl)-1-propene	3.22	16
$\gamma$ -Keto- $\gamma$ (2,4-Dimethoxyphenyl)- $\alpha$ (2-furanyl)-1-propene	3.90	16
$\gamma$ -Keto- $\gamma$ (4-nitrophenyl)- $\alpha$ (2-furanyl)-1-propene	4.97	16
$\gamma$ -Keto- $\gamma$ -phenyl- $\alpha$ (5-nitro-2-furanyl)-1-propene	2.91	16
$\gamma$ -Keto- $\gamma$ (4-methoxyphenyl)- $\alpha$ (5-nitro-2-furanyl)-1-propene	3.23	16
$\gamma$ -Keto- $\gamma$ (2,4-dimethoxyphenyl)- $\alpha$ (5-nitro-2-furanyl)-1-propene	5.17	16
$\gamma$ -Keto- $\gamma$ (4-nitrophenyl)- $\alpha$ (5-nitro-2-furanyl)-1-propene	4.86	16
$\tau$ -Keto- $\alpha$ , $\gamma$ -di(2-furanyl)-1-propene	3.17	16



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CHAPTER - 14

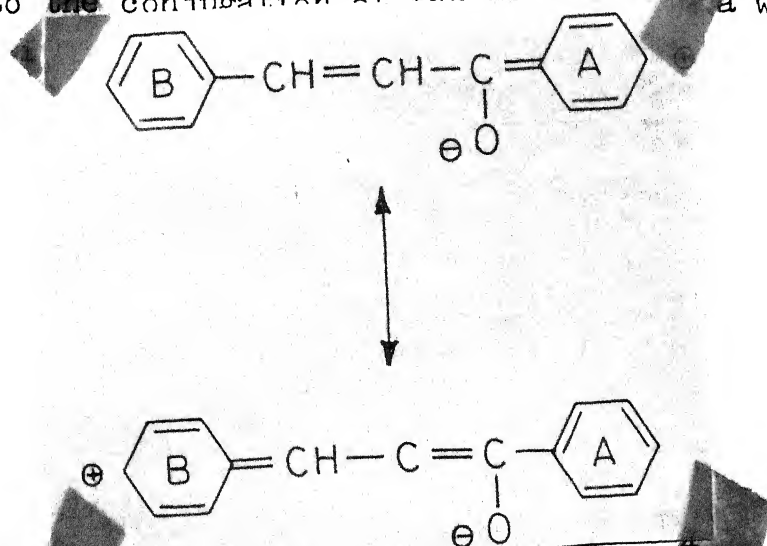
## SPECTROSCOPIC STUDIES OF CHALCONES AND THEIR DERIVATIVES

Ultraviolet Spectroscopy.....	261
Introduction.....	261
Substituent Effects on U.V. Absorption of Chalcones...	262
Solvent Effects.....	262
Miscellaneous Studies.....	262
Infrared Spectroscopy.....	263
Carbonyl Group, Substituent Effects.....	263
Hydrogen Bonding.....	263
Basicity.....	264
Rotational Isomers.....	264
Raman Spectroscopy.....	264
Nuclear Magnetic Resonance Spectroscopy.....	265
Chalcones and Their Heterocyclic Analogues.....	265
Chalcone Derivatives.....	265
Mass Spectrometry.....	266
Chalcones.....	266
Chalcone Epoxides.....	268
References.....	268

## ULTRAVIOLET SPECTROSCOPY

### Introduction:

Trans-chalcone usually shows two absorption bands<sup>1</sup> located at 300 nm (Band I) and 230 nm (Band II) respectively. Previously these bands were believed to originate due to the presence of two chromophoric groups,<sup>2</sup> viz., benzoyl and cinnamoyl moieties, in the chalcone molecule. According to the accepted view,<sup>3</sup> band I arises due to the conjugation of the molecule as a whole, thus:



The third band at 280 nm has also been reported<sup>4</sup> and has been characterised as the modified E-band of the phenyl group.

Another band located between 250-270 nm (middle band) has been observed in cis-chalcones,<sup>2,3,5-8</sup> as well as in some trans-isomers.<sup>1</sup> It has been reported<sup>9</sup> that the U.V. spectrum of cis-chalcone contains styrene absorption bands which are absent in the spectrum of trans-chalcone.

The electronic absorption spectra have been calculated for chalcone,<sup>10</sup> its derivatives,<sup>11</sup> and the heterocyclic analogues

of chalcone.<sup>12</sup> On the basis of theoretical calculations it has been shown<sup>13</sup> that the long wave ultraviolet absorption bands of 4-substituted chalcones are more complex in nature. There exist other bands besides those arising due to intramolecular charge transfer transition.

#### Substituent Effects on U.V. Absorption of Chalcones<sup>4,14-17</sup>:

In general, substitution in ring B causes greater bathochromic shift of band I, than in ring A.<sup>4,14,15</sup> Electron withdrawing substituents in ring B produce large hypsochromic effect,<sup>16</sup> but when present in ring A they exhibit bathochromic effects.

Replacement of the phenyl moiety (ring A or ring B) with 2-thienyl or 2-furyl gives rise to a bathochromic shift of band I.<sup>3,18,19</sup> The effect, however, is more pronounced when the phenyl group (ring B) is substituted by the heterocyclic residue.<sup>19</sup>

#### Solvent Effect:

The effect of solvent on the position of  $n-\pi^*$  and  $\pi-\pi^*$  transition in chalcone derivatives has been studied.<sup>20</sup>

#### Miscellaneous Studies:

The ultraviolet absorption studies are reported for the following compounds: chalcones,<sup>1-3,8,10,13,15,21-57</sup> heterocyclic analogues of chalcone,<sup>16,19,58-69</sup> chalcone glucosides,<sup>70</sup>

chalcone complexes with boron trifluoride,<sup>71</sup> ferric chloride,<sup>37,72</sup> antimony pentachloride<sup>72</sup> and boric acid,<sup>41</sup> chalcone-2,4-dinitrophenyl-hydrazones<sup>73-76</sup> and chalcals.<sup>77</sup>

### INFRARED SPECTROSCOPY

Several studies in respect of infrared absorption of chalcones,<sup>78-86</sup> heterocyclic analogues of chalcones<sup>9,87-91</sup> and chalcone derivatives<sup>92</sup> have been published.

#### Carbonyl Group, Substituent Effects:

The integral intensities of carbonyl absorption band in the infrared spectra of chalcone, 4- and 4'-substituted chalcones, as well as heterocyclic analogues (selenienyl, thienyl and furyl) have been reported.<sup>93</sup>

The frequency of carbonyl absorption in chalcone has been determined by 'Huckel's Molecular Orbital Method' as well as on the basis of other theoretical calculations.<sup>94</sup>

The substituent effects on the carbonyl stretching frequency of chalcone<sup>95-98</sup> and its heterocyclic analogues<sup>90,93</sup> have been published.

#### Hydrogen Bonding:

The effect of hydrogen bonding, viz., intermolecular and intramolecular type, on the carbonyl group of hydroxychalcones have been described in the literature.<sup>96,99,100</sup>



The intramolecular hydrogen bonding in respect of cis- and trans-isomers of 2'-hydroxy-3'-nitrochalcone has been studied.<sup>101</sup> In the cis-isomer, the hydroxyl and the nitro groups are hydrogen bonded, while in the trans-isomer the 2'-hydroxyl group is chelated with the carbonyl group.<sup>101</sup>

In the case of 2'-hydroxychalcone, the hydrogen bond energy has been calculated.<sup>95</sup>

#### Basicity:

Infrared absorption data has been used for comparison of relative basicities of chalcones,<sup>102-104</sup> ferrocene<sup>105</sup> and thiophene<sup>106</sup> analogues of chalcone.

#### Rotational Isomers:

Infrared spectroscopy has been employed in studying the rotational isomers (S-cis and S-trans) of substituted chalcones<sup>107-117</sup> and heterocyclic analogues of chalcone.<sup>105,118</sup>

#### Raman Spectroscopy:

The Raman spectrum of chalcone has been reported<sup>119-121</sup> in the literature.

## NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

### Chalcones and Their Heterocyclic Analogues:

The proton magnetic resonance spectra of some chalcones<sup>122</sup> and their heterocyclic analogues (containing furan, thiophene and selenophene ring attached at 2-position) are reported<sup>123</sup> in the literature.

The correlation between the N.M.R. signals of the hydroxyl groups of chalcone derivatives (in acetone solvent) and the  $\sigma$ -substituent parameters have been reported.<sup>124</sup>

<sup>13</sup>C-N.M.R. chemical shifts of substituted chalcones,<sup>125</sup> as well as those of heterocyclic analogues of chalcone<sup>126</sup> are available in the literature. <sup>13</sup>C<sup>NMR</sup> and PMR spectra have been studied<sup>127</sup> for ferrocenyl chalcone and their iron carbonyl complexes. It has been stated that the conjugation in the chalcone molecule is reduced by its coordination with the iron carbonyl. Based on <sup>13</sup>C-N.M.R. data, the effect of the ferrocenyl group on the  $\pi$ -electron distribution in chalcone, has been studied.<sup>128</sup>

### Chalcone Derivatives:

From the examination of N.M.R. spectra of some substituted chalcone epoxides, the following conclusions have been drawn.<sup>129</sup>

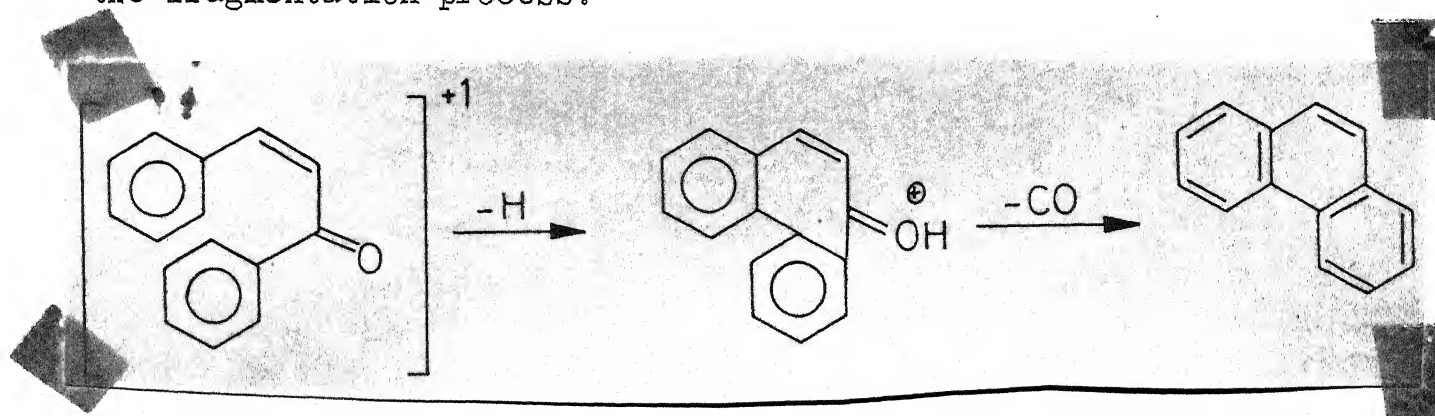
The epoxide ring has a trans configuration and the two oxirane ring protons appear in the range 5.70-5.82  $\tau$  and 5.82-6.02  $\tau$  respectively.

N.M.R. data<sup>92,130</sup> are available for isocyanato-halochalcones, trans-chalcone-oxime, semicarbazone, thiosemicarbazone 3,5-diphenyl-1-acetamido (and thioacetamido)-2-pyrazolines.

### MASS SPECTROMETRY

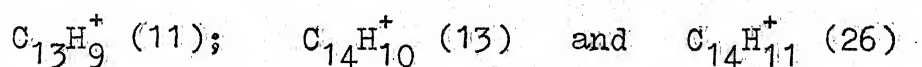
#### Chalcones:

The mass spectrum of chalcone shows three favoured ions, viz.,  $M^+$ ,  $(M-1)^+$  and  $(M-29)^+$ , where  $M^+$  stands for the molecular ion. The following mechanism<sup>131</sup> has been advanced to explain the fragmentation process:

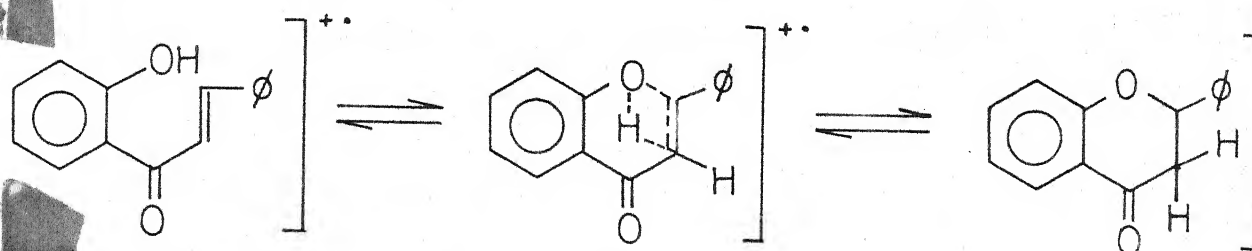


The first step is the loss of hydrogen, since it permits the formation of an extra bond. This is followed by the loss of carbon monoxide leading to the fused ring structure (vide supra).

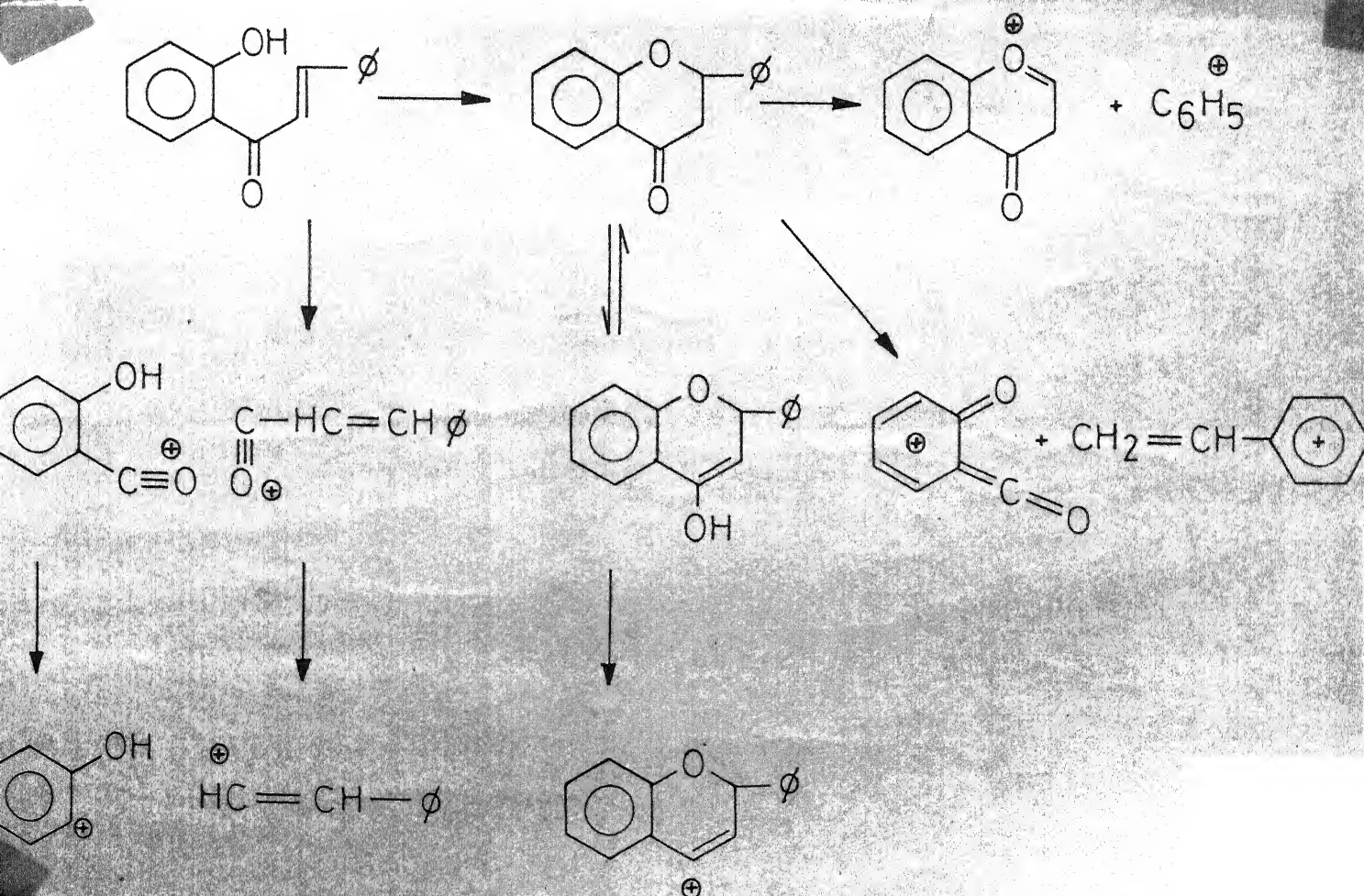
Skeletal rearrangements occur in the mass spectrometry of chalcone. The following rearrangement ions are reported,<sup>132</sup> with their relative abundance (expressed as %).



It has been shown<sup>133,134</sup> that electron bombardment of 2'-hydroxychalcone leads to the formation of flavanone. The mechanism<sup>133</sup> involves the migration of the phenolic hydrogen to the 3-position of the flavanone type ion:



The main fragmentation path of 2'-hydroxychalcone is illustrated<sup>135</sup>:



Based on mass spectrometric data, ionization potential of 4- and 4'-monosubstituted chalcones have been determined. The values so obtained are reported<sup>136</sup> to be in agreement with the values arrived at by molecular orbital calculations.

#### Chalcone Epoxides:

Mass spectrometry has been utilized<sup>137</sup> for the qualitative characterization of the transmission effects through the oxirane ring of chalcone epoxide.

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CHAPTER - 15

## CHROMATOGRAPHIC SEPARATION OF CHALCONES FROM OTHER FLAVONOIDS

Column Chromatography.....	280
Thin-Layer Chromatography.....	281
Paper Chromatography.....	281
Ion-Exchange Chromatography.....	282
References.....	282

Column Chromatography:

Column chromatography over silica gel, involving the use of berberine as a fluorescent adsorbent, has been employed<sup>1</sup> successfully for the separation of chalcone from 4-methoxy-chalcone.

2'-Hydroxychalcone are separable from the corresponding flavanones, e.g., butin from butein, by column chromatography using polyamide<sup>2</sup> as adsorbent. 2'-Hydroxychalcones are retained by the column, while flavanones are eluted with aqueous methanol. The chalcones, adsorbed on the column, are then eluted with the pure solvent. The separation of 2'-hydroxychalcones from flavanols<sup>3</sup> and flavanonols<sup>3</sup> have likewise been carried out by polyamide column chromatography.

### Thin Layer Chromatography:

Thin layer chromatography (TLC) on silica gel or polyester film has been used<sup>4</sup> for effecting the separation of chalcones from other flavonoids and alkaloids. Hesperidin methyl chalcone in pharmaceuticals has been isolated<sup>5</sup> on polyamide thin layers and subsequently estimated by fluorometric method (treatment of the chalcone-spot with methanolic aluminium chloride, and the fluorescent spot removed, extracted with a solvent and subjected to spectrophotometric analysis).

A preparative TLC method has been developed<sup>6</sup> for the separation on silica gel, of several hydroxychalcones and their corresponding flavanones, using ligroin-ethylacetate as the developer solvent.

The cis-trans isomers of 2-hydroxy- $\alpha$ -methoxychalcone have been separated<sup>7</sup> on silica gel plates using elutropic solvent, benzene-methanol (95:5).

$R_f$  values are reported for a large number of substituted aromatic chalcones,<sup>8-10</sup> ferrocene,<sup>11</sup> furyl,<sup>10</sup> thienyl<sup>9,10</sup> and pyrrolyl<sup>9</sup> analogues of chalcones. The  $R_f$  values have been correlated<sup>8</sup> with the position and nature of the substituents.

### Paper Chromatography:

Chalcones have been separated from other flavonoids by paper chromatography<sup>12-14</sup> using butanol-acetic acid-water (4:1:2.2) as the developer solvent. The spot positions of

chalcones on the chromatogram are revealed either by characteristic fluorescence in the ultraviolet light or by colour reactions.

Paper chromatography of some chalcones<sup>15,16</sup> and their glycosides<sup>15</sup> are reported. These give yellow or orange spots on paper developed with aqueous phenol.<sup>15</sup>

Paper chromatography, involving the use of boric acid-sodium acetate impregnated paper, has been utilized<sup>17</sup> for differentiating *o*-dihydroxyflavanones from similar flavanones-but lacking in catechol type hydroxylic grouping.

Relation between chromatographic parameters of halogenated chalcones by adsorption and partition chromatographic techniques have been studied.<sup>18</sup>

#### Ion Exchange Chromatography:

Chalcone is reported<sup>19</sup> to be quantitatively adsorbed on the anion exchange resin (Amberlite IRA-400, in  $\text{HSO}_3^-$  form), provided the passage through the column is long and can be eluted with sodium chloride solution.

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49, 1483<sup>i</sup> (1955).

## P A R T - I V

CHAPTER - 16

## NATURALLY OCCURRING CHALCONES AND THEIR DERIVATIVES

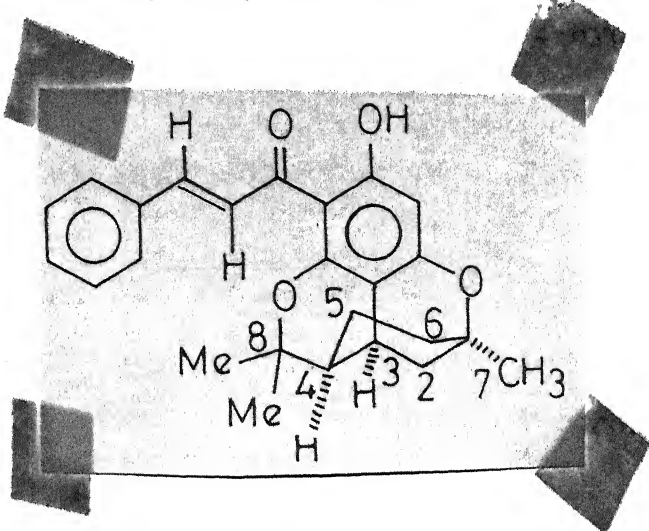
During the past decade a number of reports have appeared in the literature, describing the isolation of chalcones from the various parts of the plants, viz., roots,<sup>6,19,20,24,82,83</sup> heart-wood,<sup>44,73,79,80</sup> buds,<sup>4</sup> leaves,<sup>23,27,29,34,36,51,52,54,58,71</sup> blossoms,<sup>45-47</sup> inflorescences,<sup>33</sup> flowers<sup>2,8,17,18,23,29,42</sup> and seeds.<sup>5,53,57,71,74</sup> These compounds exist in the free state as chalcones or in the combined form as glycosides. The substituent(s), viz., hydroxy, methoxy, methyl and isopentenyl, may be present either in ring A and/or ring B of the chalcone molecule. Besides, there are reports<sup>58,66,70,76,82-85</sup> about the isolation of dihydrochalcones from the higher plants.

Table I lists (vide infra) the naturally occurring chalcones and their derivatives.

Table I

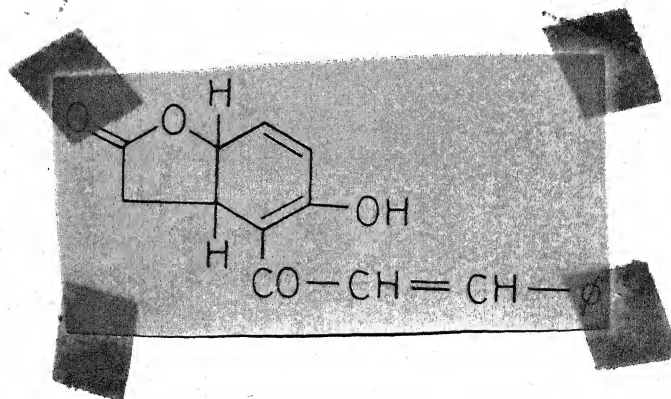
Naturally occurring chalcones and their derivatives

<u>Source</u>	<u>Chalcones and their derivatives</u>	<u>Ref.</u>
<u>Acacia</u> <u>auriculiformis</u>	2',3',4',4-Tetrahydroxychalcone	1
<u>Acacia cyanophylla</u> (Flowers)	Chalcononaringenin-4-glucoside, Isosalipurposide	2

<u>Adenanthera pavonina</u>	Chalcone and	
"Red Sandalwood"	2',3,4,4'-Tetrahydroxychalcone (Butein)	3
<u>Alnus virdis</u> (Buds)	4',5'-Dihydroxy-6'-methoxychalcone	4
<u>Alpinia speciosa</u> (Seeds)	2',4'-Dihydroxy-6'-methoxychalcone (Cardamonin)	5
<u>Angelica keiskei</u> (Roots)	Prenyl chalcones: Xanthoangelol and hydroxy derricin	6
<u>Aniba rosaeodora</u> DUCKE		7
		
<u>Antirrhinum majus</u> (Yellow flowers)	Chalcononargenin-4'-glucoside, 2',3,4,4',6'-Pentahydroxychalcone- 4'-glucoside	8
<u>Berchemia zeyheri</u> "Red ivory" (Red-wood)	$\alpha$ , 2',4,4',6'-Pentahydroxychalcone	9



<u>Bidens tripartite</u>	2,3',4,4'-Tetrahydroxychalcone, Butein-7-O- $\beta$ -D-glucopyranoside	10
<u>Chromalaena odorata</u>	2',4-Dihydroxy-4',5',6'- trimethoxychalcone, 2'-Hydroxy- 4,4',5,5',6'-pentamethoxychalcone	11
"Citrus Molasses"	A Methylchalcone	12
<u>Cordia alliodora</u> (Lonchocarpus)	Cordoin, Isocordoin, $\Psi$ -Isocordoin, Dihydrocordoin, Derricin, 4-Hydroxy- derricin, Lonchocarpin, 4-Hydroxy- lonchocarpin and 4-Hydroxy- isocordoin	13-16
<u>Coreopsis tinctoria</u> (Ray flowers)	4'-Glucosidoxy-2',3',3,4-tetra- hydroxychalcone (Marein)	17
"Cotton" (Flowers)	2',3',4',6',8',3,4-Heptahydroxy- chalcone glucoside	18
<u>Cryptocarya</u> <u>bourdillonii</u> (Lauraceae) Roots		19,20



Daemonorops dracu 2,4-Dihydroxy-5-methyl-6-methoxy 21  
 "Dragon's blood : chalcone; 2,4-Dihydroxy-6-methoxy-  
 resin" chalcone  
 Fruit

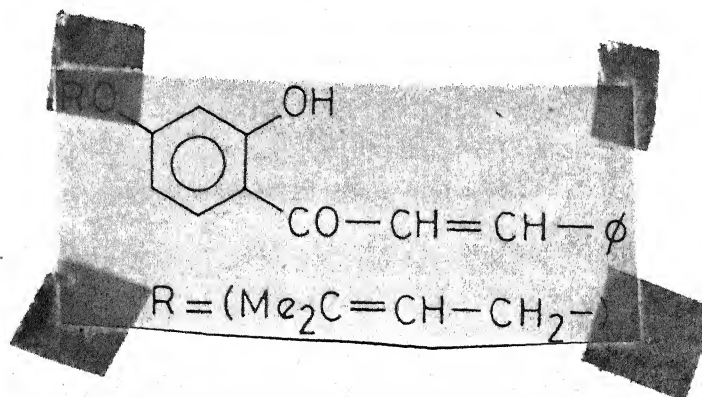
Dahlia species 4'-Arabinosylgalactoside of butein 22  
 and other glycosides

Dahlia tenuicaulis 2'-Hydroxy-4,4',6'-trimethoxy- 23  
 (Leaves) chalcone

Dahlia tenuicaulis 4,2',4'-Trihydroxychalcone, 23  
 (Flower heads) 3,2',4'-Trihydroxy-4-methoxychalcone

Datisca cannabina Unidentified chalcone 24  
 (Root cortex)

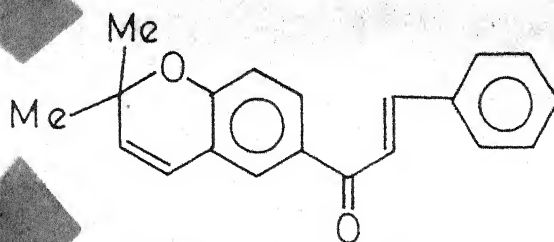
Derris sericea 25  
 (Root bark)



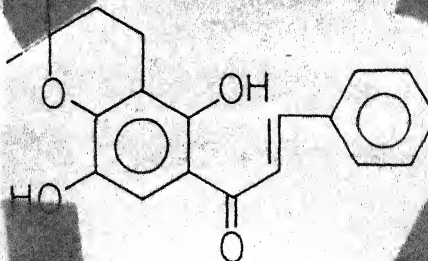
Didymocarpus 2',6'-Dihydroxy-4',5'-dimethoxy- 26  
pendicellata chalcone  
 (Gesneriaceae) (Pashanone)  
 Roots

Eupatorium odoratum 2'-Hydroxy-4,4',5',6'-tetramethoxy- 27  
(Leaves) chalcone

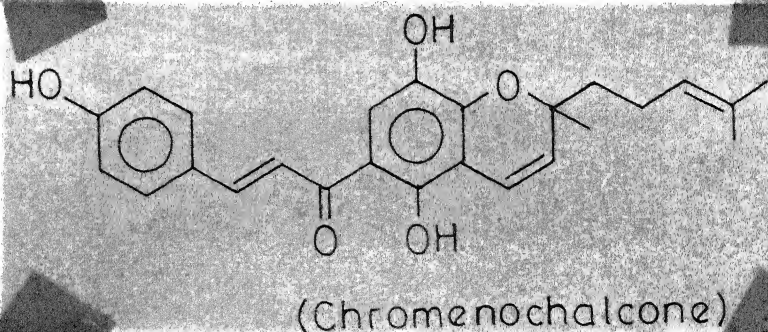
Flemingia Chappar 2',4'-Dihydroxychalcone, 28-32  
Ham. 2',4',4'-Trihydroxychalcone,  
(Whole plant) 2',4'-Dihydroxy-5'-methoxychalcone



Flemingia Chappar 4',6'-Dihydroxy-3'-methoxychalcone 29  
Ham.  
(Flower/leaves)



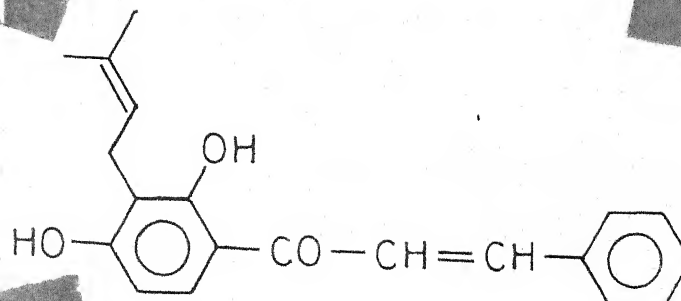
Flemingia congesta  
(Inflorescences)



Flemingia stricta

(Leguminosae)

(Leaves)



Flemistrictin-A

34

Flemingiastrobilifera

(Roots)

3',6'-Dihydroxy-2',4',5',4-  
tetramethoxychalcone

35

Flemingia wallichii

(Leaves)

Homoflemingin,  
Flemiwallichin

36

Glycyrrhiza echinata

(Tissue culture)

4,4'-Dihydroxy-2-methoxychalcone  
(Echinatin)

37

Glycyrrhiza glabra

(Roots)

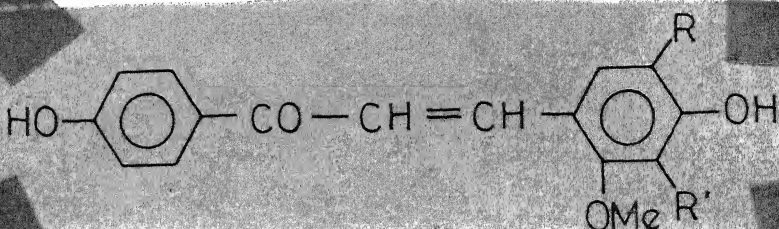
2,4,4'-Trihydroxychalcone, 4-  
Hydroxychalcone, Unidentified  
chalcones,  
Glycosidal chalcone

38,39

40

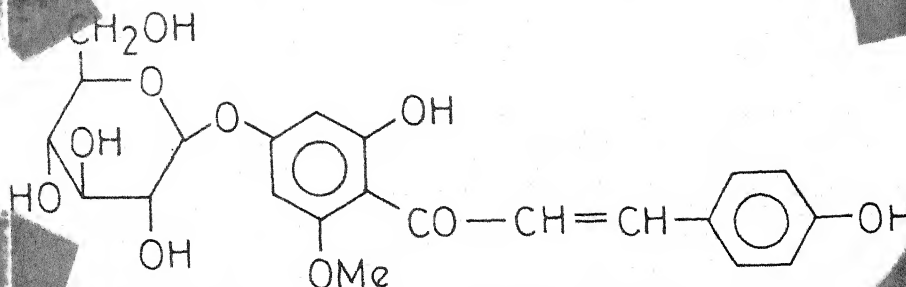
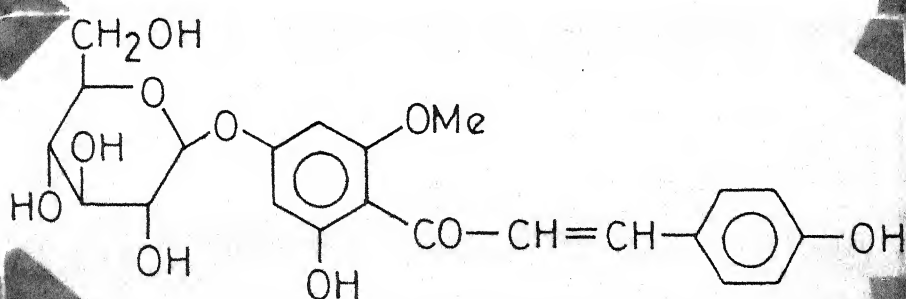
Glycyrrhiza glabra

(Root bark)

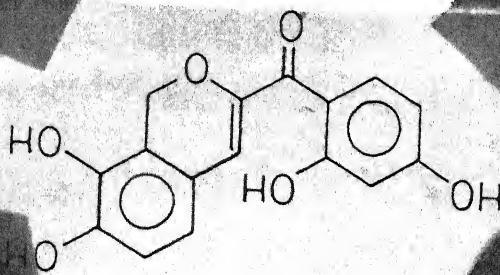
I, R = (CMe<sub>2</sub>-CH=CH<sub>2</sub>); R'=H

Gnaphalium affine

(Flowers)

Gnaphalium multicepsGoniorrhachismarginata

(Heartwood)

Helichrysumbracteatum

(Blossoms)

2',3,4,4',6'-Pentahydroxychalcone-

45-47

2'-glucoside, Isosalipurposide,

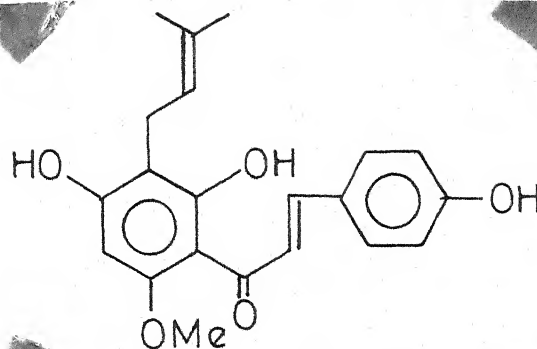
2,3,4,4',5,6'-Hexahydroxychalcone-

2'-glucoside

"Hop extract"

293

48



(Xanthohumol)

Larrea nitida

(Aerial parts)

2',4'-Dihydroxy-3'-methoxychalcone

49

(Larrein)

2',4'-Dihydroxychalcone

Lasthenia

(Compositae)

Butein and Okanin

50

Lindera umbellata

Thumb (Leaves)

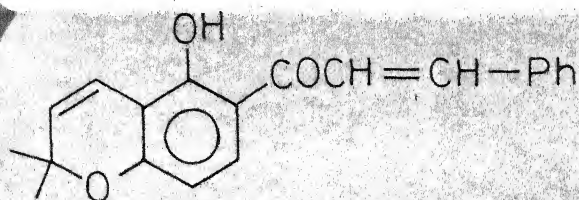
2',6'-Dihydroxy-4'-methoxychalcone

51-52

Lonchocarpus sericeus

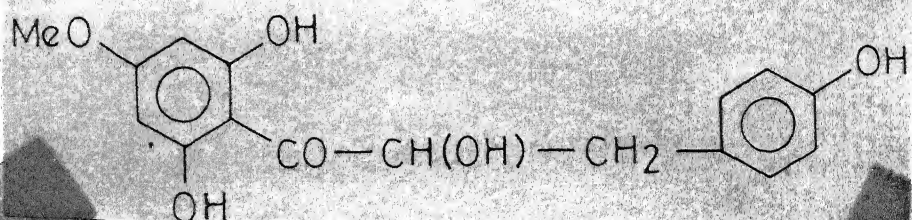
(Belgian Congo)

Seeds and roots



Lyonia formosa

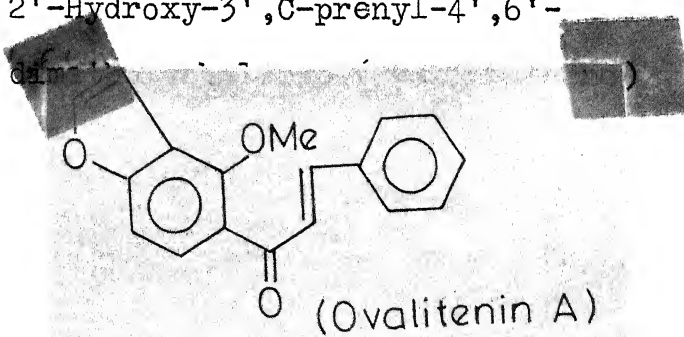
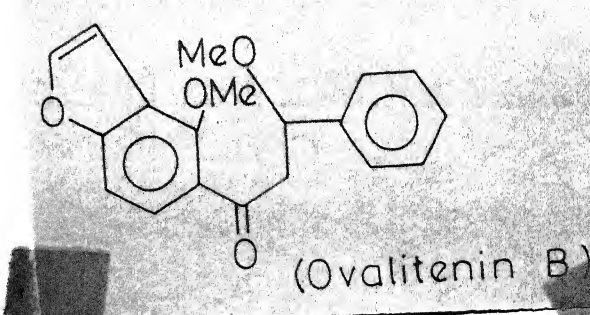
(Leaves)



(Lyonogenin)

and Lyonogenin-2'-glucopyranoside

(Lyonotin)

<u>Machaerium</u> <u>nucronulatum</u> (Wood)	Butein and Isoliquiritigenin	55
<u>Merrillia caloxylon</u> (Fruit)	2'-Hydroxy-3,4,4',6'-tetramethoxy- chalcone, 2',3-Dihydroxy-4,4',6'-trimethoxy- chalcone, 2-Hydroxy-3,4,4',5',6'-pentamethoxy- chalcone	56
<u>Milletia ovalifolia</u> (Seeds)	2'-Hydroxy-3',6'-prenyl-4',6'-  (Ovalitenin A)  (Ovalitenin B)	57
<u>Myrica gale</u> (Leaves)	2',4'-Dihydroxy-6'-methoxy-3',5'- dimethylchalcone	58
<u>Myrica gale</u> (Fruits)	2'-Hydroxy-4',6'-dimethoxy-3'- methyl-dihydrochalcone	58

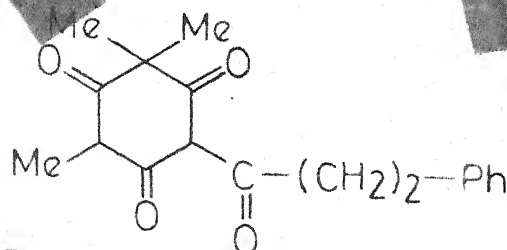
Myrica gale

(Fruits)

2',6'-Dihydroxy-4'-methoxy-3',5'-

59

dimethyl-dihydrochalcone.

Oenothera hookeri

Isosalipurposide

60

## Onagraceae

(Petals)

Onagraceae: 13 species contain the  
chalcone, while 27 species are  
lacking in it

61

Onychium auratum

(Fern)

2',6'-Dihydroxy-4',5'-dimethoxy-  
chalcone,

62

2',6'-Dihydroxy-4'-methoxychalcone

63

Petunia hybrida

(Pollen)

4,2',4',6'-Tetrahydroxychalcone

64

Piper methysticum

Forst,

(Roots)

2',4'-Dihydroxy-4,6-dimethoxychalcone

65

Pityrogrammaaustroamericana

(Gold-fern)

(Yellow powdery

coating on the

underside of fronds)

2',6'-Dihydroxy-4,4'-dimethoxy-  
chalcone,

66

2',6'-Dihydroxy-4,4'-dimethoxy-  
dihydrochalcone



<u>Pityrogramma</u> <u>calomelanos</u> and P. tarterea (Exudate) (Jamaican ferns)	2',6'-Dihydroxy-4'-methoxy- dihydrochalcone,  dihydrochalcone	67
<u>Pityrogramma</u> <u>chrysophylla</u> heyderi (Fronds)	2',6'-Dihydroxy-4'-methoxychalcone 2',6'-Dihydroxy-4,4'-dimethoxy- chalcone	66 68
<u>Pityrogramma</u> <u>lehmanii</u> (Silver fern)  White coating on the underside of fronds	2',6'-Dihydroxy-4,4'-dimethoxy- dihydrochalcone	66
<u>Pityrogramma</u> <u>triangularis</u> (Ferns) Exudate	2',6'-Dihydroxy-3'-methyl-4'- methoxychalcone	69
<u>Podocarpus nubigena</u>	2,2',4,4',6'-Pentahydroxy-dihydro- chalcone (Nubigenol)	70
<u>Polygonum senegalese</u> (Seeds and leaves)	2',4'-Dihydroxy-3',6'-dimethoxy- chalcone	71
"Populus bud oils" (Several species or	2',4',6'-Trihydroxychalcone, 2',6'-Dihydroxy-4'-methoxychalcone	72

Prunus cerasus L.

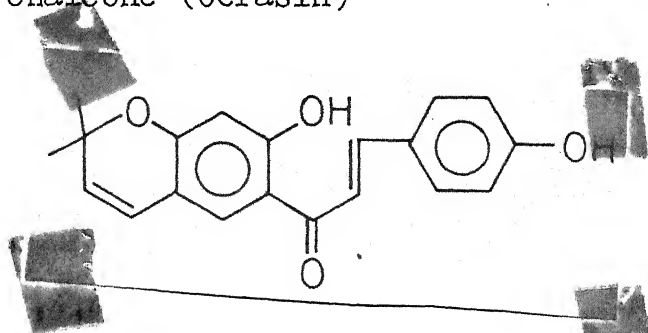
(Heartwood)

2'-Hydroxy-2,4,4',6'-tetramethoxy-  
chalcone (Cerasidin)

73

2',4'-Dihydroxy-2,4,6'-trimethoxy-  
chalcone (Cerasin)Psorelea corylifolia

(Seeds)



Isobavachalcone,

74

4'-O-Methylchalcone,

5'-Formyl-2',4-dihydroxy-4'-  
methoxychalcone

75

Rhododendroncanescens,R. nudiflorum andR. roseum2',4,6'-Trihydroxy-4'-methoxy-  
dihydrochalcone and Asebotin

76

Salix acutifolia

(Bark)

2',4,4',6'-Tetrahydroxychalcone-6'-  
(6-O-p-Coumaroyl)-D-glucopyranoside,  
Chalconaringenin-6'-D-glucoside

77

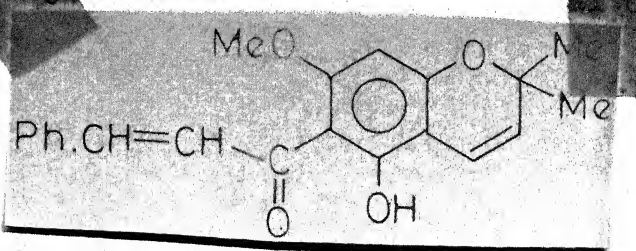
Tephrosia obovata

Merr.

(Fish Poison Plant)

Pyranochalcone

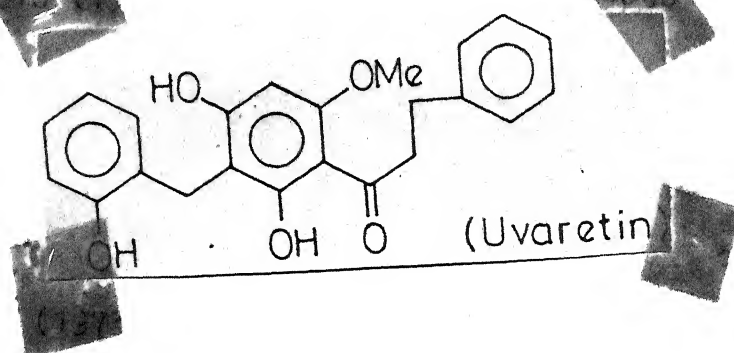
78



Trechylodium  $\alpha$ , 2', 3, 4, 4'-Pentahydroxychalcone 79, 80  
verrucosum  
 (Gaertn.) oliv.  
 (Heartwood)

Tulipa CV. "Apeldoorn" 2', 3, 4, 4', 6'-Pentahydroxychalcone 81  
 (During development of Anthers) 2', 4, 4', 6'-Tetrahydroxy-3-methoxy-  
 chalcone,  
 2, 4, 4', 6-Tetrahydroxychalcone

Uvaria acuminata 82  
 (Roots)



Uvaria chamae Benzylidihydrochalcones: 83  
 Chamuvarin and chamuvaritin

Viburnum davidii 2', 4, 4'-Trihydroxy-dihydrochalcone 84

Viburnum davidii Davidioside, 85  
 (Leaves) Davidigenin and 4'-methoxy derivative

Viseum album L. 2'-Hydroxy-4', 6'-dimethoxychalcone 86

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CHAPTER - 17

## BIOLOGICALLY ACTIVE CHALCONES AND THEIR DERIVATIVES

Introduction.....	307
Bacteriostatic or Bactericidal Activity.....	308
Antimicrobial Activity.....	312
Antibiotic Activity.....	312
Tuberculostatic and Anti-tubercular Activity.....	313
Antiparasitic Activity.....	314
Antimalarial Activity.....	314
Acaricidal Activity.....	315
Schistosomicidal Activity.....	315
Anthelmintic Activity.....	315
Insect Repellant and Insecticidal Activity.....	315
Toxicity to Animals.....	316
Herbicidal Activity.....	316
Fungistatic and Fungicide Activity.....	316
Action on Enzymes.....	317
Antipeptic Ulcer Activity.....	319
Hypotensive/Antihypertensive Activity.....	320
Antitumor/Cytotoxic Activity.....	321
Choleretic/Hypocholeretic Activity.....	322
Spasmolytic Activity.....	323
Antispasmodic and Tranquilizing Activity.....	324
Anti-inflammatory Activity.....	325
Analgesic and Sedative Action.....	325

Antithrombic Activity.....	325
Capillary Fragility.....	325
Vasodilatory Activity.....	326
Estrogenic Activity.....	327
Anesthetic Activity.....	327
Anticoagulating Effect.....	327
Anticonvulsant/Narcotic Potentiation Activity.....	328
Therapeutic Activity.....	328
Antiangiotensin/Antiarrythmic/Diuretic Activity.....	328
Miscellaneous Biological Activities.....	329
Action on Spermatocytic Chromosomes.....	331
Decrease in the Incidence of Blood Spots in Chicken Eggs.	331
Plant Growth Inhibiting Activity.....	331
References.....	332

### Introduction:

The presence of enone function in chalcone molecule confers upon it the antibiotic activity<sup>1-35</sup> (bacteriostatic/bactericidal). This property is enhanced when substitution is made at the  $\alpha$ - (nitro and bromo) and  $\beta$ -(bromo and hydroxylic) positions.<sup>27</sup> Some substituted chalcones and their derivatives, including some of their heterocyclic analogues, have been reported to possess some interesting biological properties, which are detrimental to the growth of microbes,<sup>23-26</sup> tubercle bacilli,<sup>30-35</sup> malarial parasites,<sup>37</sup> acrus,<sup>38</sup> Schistosoma<sup>39</sup> and intestinal worms.<sup>25,40,41</sup> Some of the compounds are claimed to be toxic to animals<sup>30,36</sup> and insects<sup>42,43</sup> and are also reported to exhibit inhibitory action

on several enzymes,<sup>53-61</sup> fungi<sup>1,3,17,22,48-51</sup> and herbaceous plants.<sup>43,47</sup> The compounds of the chalcone series also show profound influence on the cardio-vascular cerebro-vascular and neuromuscular systems, including the vital organs of the experimental animals.<sup>63-125</sup> ~~63-67,77-117,119-125~~ The data on the biological activities of these compounds are summarized in Table I.

Table I

Biological Activities of Chalcones

Bacteriostatic or Bacteriocidal Activity

<u>Compound</u>	<u>Remarks</u>	<u>Test organism</u>	<u>Ref.</u>
Chalcone	Significant bacteriostatic action.	E. coli S. aureus B. mycoides B. subtilis S. lutea	1
Chalcone	The bacteriostatic effect could not be reversed by cystein, in contrast to the effect of this compound on other antibiotics.	S. aureus	2
Chalcone	The antibacterial action is associated with $\alpha, \beta$ - unsaturated carbonyl group of the molecule.	S.aureus 209P E.coli T.mentagrophytes C.albicans W.anomala T.utilis A.usami P.chrysogenum Q 176 S.sake	3

Prenylated chalcone	4-Hydroxyderricin  exhibits a marked inhibi-  tory activity (in vitro).	Gram-positive microorganisms	4
Halohydroxy- chalcones	Chalcones having 4'- hydroxyl and halogenic substituents (in 2- and 4- positions) possess marked antibacterial activity.  Also the chalcones with fluoro substituent have better antibacterial activity compared to bromo- or chloro-chalcones.	S. albus S. aureus	5
Nitrohydroxy- chalcone	3'-Nitro-4'-hydroxy-2- methoxy chalcone has the highest antibacterial acti- vity (vivo). Other active chalcones are: 3'-nitro- 4'-hydroxy-2,3-dimethoxy- chalcone and 3'-nitro-4'- hydroxy-2,5-dimethoxy- chalcone.	S. albus	6,7

Nitrohydroxy-chalcones	The following chalcones exhibit antibacterial activity:	E. coli S. flexneri K. pneumoniae S. aureus and S. albus	8
	$\text{RCOCH}=\text{CHC}_6\text{H}_4\text{OMe-m}$	strain resistant	
	R=2,5-, 4,3-, 4,2-, and 2,4-(OH)NO <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	to streptomycin and polymyxin	
Nitrohydroxy-chalcone	3'-Nitro-4'-hydroxy-2-methoxy-chalcone has a strong antibacterial action.	S. albus (in vitro)	7
Aminochalcones	4- (and 4')-amino chalcones possess bacteriostatic activity.	S. aureus S. hemolyticus	9
Chlorohydroxy-chalcone	Antibacterial	-	10,11
Bromohydroxy-chalcone	Antibacterial	S. aureus	12
Bromohydroxy-chalcone	4',5-Dibromo-2-hydroxy-chalcone has the highest bacteriostatic activity (1:640,000).	-	13
Bromohydroxy-chalcone	2,2'-Dihydroxy-3,5,5'-tri-bromo-chalcone possesses bacteriostatic action. Inhibitory concentration: 1:640,000.	S. aureus	14

Iodohydroxy-chalcone	4'-Hydroxy-3',4,5'-tri-iodochalcone, 4'-Hydroxy-3',5'-diiodo-4-propoxy (and 4-butoxy)-chalcones and considered as possible antibacterial agents.	-	15
Alkylthio-chalcones	The following chalcones possess antibacterial activity (in vitro): 4'-Thioalkylchalcone and 4-chloro-5'-methyl-2'-thioalkyl chalcone.	B. subtilis NRRL E. coli 0-55 S. aureus 209P	16
Sulphonic acid and carboxylic acid derivatives of chalcones	Bactericidal	-	17
Chalcone sulphanilamides	Potential antibacterial agents.	-	18
Chalcone penicillanate	2-Fluoro-3-nitro-4-chalconyl-6-phenylacetamido-penicillanate possesses antibacterial action.	-	19,20
Various chalcones	Bacteriostatic activity.	B. abortus	21
Furan analogues of chalcone	Significant bacteriostatic action.	E. coli S. aureus B. mycoidis B. subtilis S. lutea	1



Furan and 8-hydroxyquinoline analogue of chalcone	-	B. subtilis	22
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### Antimicrobial Activity

$\alpha$ -substituted chalcones	Activity was increased by $\alpha$ -bromination.	Trichophyton	23
Hydroxycarboxy chalcones and their dihydro derivatives	4'-Hydroxy-5'-carboxy-chalcones, 4-chloro-4'-hydroxy-5'-carboxychalcone and 4-methoxy-4'-hydroxy-5'-carboxydihydrochalcone possess antimicrobial activity (in vitro).	B. subtilis S. hemolyticus and other bacteria in vitro	24
Chalcone derivative	Methylene dithiodiacetic acid derivative (produced by the reaction of chalcone with monothiol acetic acid) has antimicrobial action.	Trichomonas vaginalis	25
$\alpha$ -Bromo-chalcones	Antimicrobial activity.	-	26

### Antibiotic Activity

Chalcone	Antibiotic activity is associated with the C=C bond of the chalcone molecule. Enhancement in antibiotic activity results when	-	27
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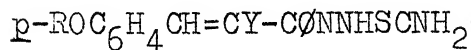
substitution is made at the  $\alpha$ -(nitro- and bromo) and  $\beta$ -(bromo- and hydroxyl) positions respectively. Addition of cystein or serum to chalcones hampers activity owing to their reduction with SH group.

Salicylic chalcones	2'-Hydroxy-4'-carbethoxy chalcone has an antibiotic activity.	-	28
Furan analogue of chalcone	Exhibits an antibiotic action.	E. coli	29

#### Tuberculostatic and Anti-Tubercular Activity

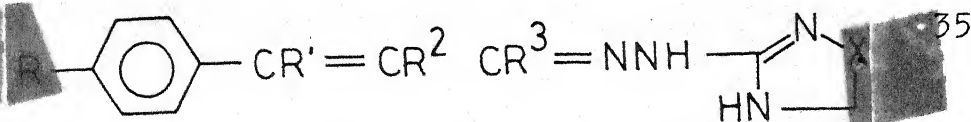
Furan analogue of chalcone	Compared to thiomicid it possesses lesser tuberculostatic action and is markedly toxic.	Rats	30
Chalcone-2-hydroxy-4-acetamido-benzene sulphonyl hydrazone	Potential anti-tubercular compound	-	31
Semicarbazone and thiosemicarbazones of chalcone or its analogue	The highly effective anti-tubercular compounds are: a) Semicarbazones of thiophene analogue of chalcone containing chloro- and nitro-substituents	Tubercle bacilli	32 33 34

b) and those corresponding  
to the general formula:



(R=alkyl, Y=MeO, COOH,  
or phenyl)

Chalcone  
derivative



R=Cl; OEt; Ph; CF<sub>3</sub>, Br; SMe;

SO<sub>2</sub>Me; Me, OC(S)NMe<sub>2</sub>;

R'=H; 4-ClC<sub>6</sub>H<sub>4</sub>; 2-naphthyl;

R<sup>2</sup>=H; Me;

R<sup>3</sup>=substituted phenyl;

2-naphthyl;

X=(CH<sub>2</sub>)<sub>1-3</sub>; CHMe

### Antiparasitic Activity

Thiophene  
analogues of  
chalcone

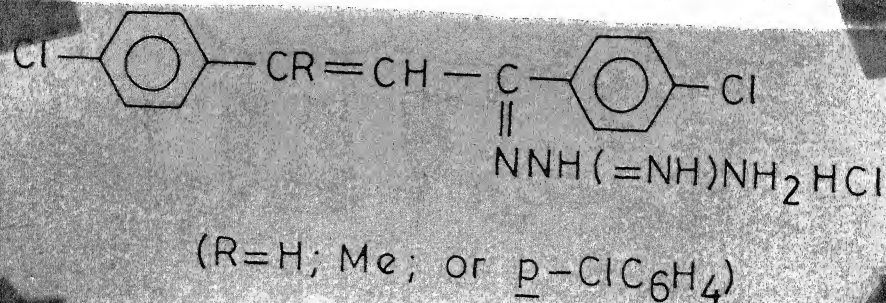
As possible antiparasitic  
compounds.

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36

### Antimalarial Activity

Chalcone  
derivatives



37

Acaricidal Activity

Chalcone and some furan analogues	Exhibit acaricidal activity.	-	38
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Schistosomicidal Activity

Chalcone derivatives	Thienyl pyrazolines derived from appropriate chalcones are described as potential schistosomicidal agents.	-	39
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Anthelminthic Activity

2',4'-Dihydroxychalcone(s) and derivatives	a) Toxicity and local irritation are less than hexylresorcinol.	Ascaris	40
	b) Chalcone derivative, viz., 3,5-diphenylisoxazoline has shown anthelmintic activity	Pin worms	41
	c) 2,2'-Dihydroxychalcone has also (in vitro) anthelmintic activity.	Am <sup>o</sup> ebae	41
Chalcone derivatives	Methylenedithiodiacetic acid derivative of chalcone possesses antiprotozoal activity.	Shigella dysenteriae	25

Insect Repellant and Insecticidal Activity

Chalcone derivatives	Some chalcone derivatives are claimed to have insect repellant properties.	-	42
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Chalcone derivatives	N-substituted <u>o</u> -carbamoyl oxime of chalcone are reported to exhibit a weak insecticidal activity.	-	43
Chalcone	Toxicity towards summer eggs and adult females of fruit tree-red spider mite.	Metatetranychus ulmi	44
Chalcone $\alpha$ , $\beta$ -dichloride and DDT	Female flies mortality is 92%.	DDT resistant female flies	45

#### Toxicity to Animals

Furan analogue of chalcone	Markedly toxic.	Rats	30
Hydroxy- and methoxy-chalcones	When all the hydroxyl groups (in the polyhydroxy-chalcone) are methylated, the toxicity increases.	Fresh water fish	46

#### Herbicidal Activity

Chalcone derivative	a) N-substituted <u>o</u> -carbamoyl oxime of chalcone exhibits weak herbicidal activity.	-	43
	b) Pyrazolium salts of chalcone are very effective as herbicides.	Lambsquarters and mustard	47

#### Fungistatic and Fungicide Activity

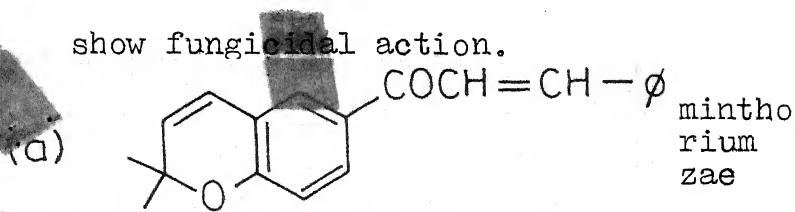
Substituted chalcones	2'-Hydroxychalcone sulphonie acid possesses a weak antifungal activity.	Mold and fungi	48
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Substituted chalcones	-	-	49
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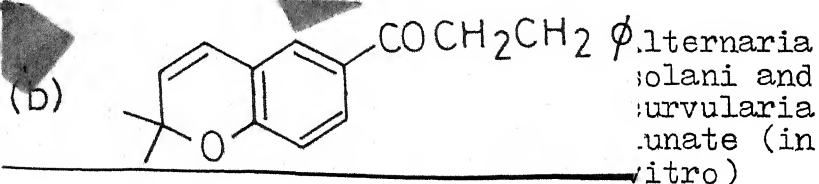
Substituted chalcones	Carboxylic and sulphonic acid derivatives of chalcone	-	17
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show fungicidal action.

Substituted  
chalcones and  
dihydro-  
chalcones



50



c) 2',4'-dihydroxy-  
dihydrochalcone.

Chalcone	Exhibits an antifungal activity.	Fungi	1,3
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Heterocyclic analogues of chalcone	Furan and 8-hydroxy- quinoline	Fungi	1,22
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α-chalcone and α-2-furan analogue of chalcone	Fungistatic activity is associated with these compounds.	F.graminearum P.digitatum and B. allii	51
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2-Hydroxy- 2'-carboxylic chalcone	Exhibits an antifungal activity.	Cucumber mildew	52
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#### Action on Enzymes

3,3',4,4'- Tetrahydroxy chalcone	Efficient inhibitor of liver xanthine oxidase activity.	Rats	53,54
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- c) 3,4-Dihydroxy-3'-carboxy chalcone; Inhibits 5-hydroxy tryptophan decarboxylate - 55,56
- b) 3,4,4'-Trihydroxy-3'-carboxy chalcone
- a) Naringenin chalcone Inhibitor of sodium-potassium dependent ATP-ase. The extent of inhibition is dependent upon the number and position of the hydroxyl groups. The para hydroxylic function of ring B (phlorizin) is involved in the inhibitory action. Pig kidney 57
- b) Hesperidin chalcone
- c) Coreopsin
- d) Phlorizin
- e) Asebotin
- Some salicylic chalcones Inhibits the aromatic L-amino-acid carboxylases, (the standard for comparison is  $\alpha$ -methyl dopa). Guinea pig kidney 58
- Chalcone and furan analogue of chalcone a) These compounds inhibit the activity of papain, and Papain 59
- b) Inhibits cholinesterase in horse serum - 55,56

c) Furan analogue of chalcone - 60

has a marked ability to inhibit the activity of enzyme dihydroxy-phenyl-alanine decarboxylase.

Various  
chalcones and  
dihydro-  
chalcones

2',4,4'-Trihydroxy chalcone Wheat root 61

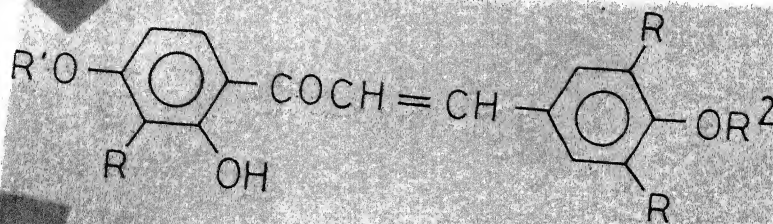
is a potent stimulator of indole acetic acid oxidase. It stimulates wheat-root growth, inhibits the absorption of sugars and of 2,4-dichlorophenoxy acetic acid and inhibits oxidative phosphorylation and gives a distinct uncoupling effect.

Resorcylic  
chalcones

Inhibitory activity on L- - 62  
dopa decarboxylase.

#### Antipeptic Ulcer Activity

Isopentenyl-  
chalcone



$\text{R}' = \text{R}^2 = \text{H};$

$\text{R} = \text{Isopentenyl}$

63-67

These compounds have proved useful in the treatment of rat stomach ulcers.



Chalcone derivatives	Useful in the treatment of gastrointestinal ulcers.	Rats	68-76
Prenyl-oxychalcones	Possess antipeptic ulcer activity.	Rat	77
Prenyl chalcones	Exhibit antipeptic ulcer activity.	Mice	78

#### Hypotensive/Anti-hypertensive Activity

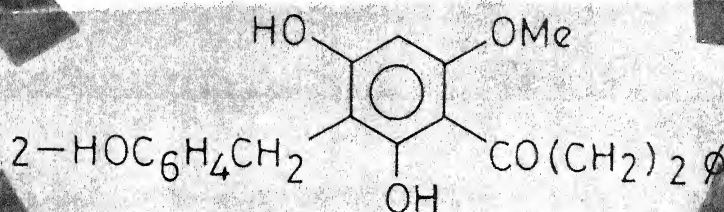
2',4',6'-Trihydroxy-chalcone	Hypotensive property is associated with this chalcone.	-	79
a) $\omega$ -Amino-alkoxy chalcones and acid addition salts	Compounds with antihypertensive properties.	-	80-84
b) N,N-Disubstituted-2-( $\omega$ -aminoalkoxy)-3',4',5'-trimethoxy-chalcone			
c) Reduced benzofuran chalcone derivative			
Indole analogues of chalcone	Weakly hypotensive.	-	85
2-[3-(4-methyl-1-piperazinyl)propoxy-4'-methyl(and 4'-chloro)] chalcone hydrochlorides and related compounds	Hypotensive action.	-	86,87

4-Aminohalo- genochalcone (without a 2'-hydroxy substituent)	Hypotensive activity	-	49
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# Antitumor Activity/Cytotoxic Activity

2,4,4'- Trihydroxy- chalcone and 2',4,4',6'- tetrahydroxy- chalcone	Antineoplastic action on Ehrlich's ascitic sarcoma in mice.	Mice	90 <del>88</del> ^
Nitrochalcones, having nitro group in 2- (and 2') and 4-(and 4'-) positions	These compounds show cytotoxic activity.	Tested against normal and Rous virus- transformed hamster fibro- blasts	89
Isothiocyanato chalcones	4-Nitro-3'-isothiocyanato- chalcone is the most active compound in respect of cytotoxicity and cancerostatic effect.	HeLa cells	90

Uvaretin (a  
dihydro-  
chalcone from  
Uvaria  
acuminata)



Uvaretin showed a anti-  
tumor activity in a lympho-  
cytic leukemia test.

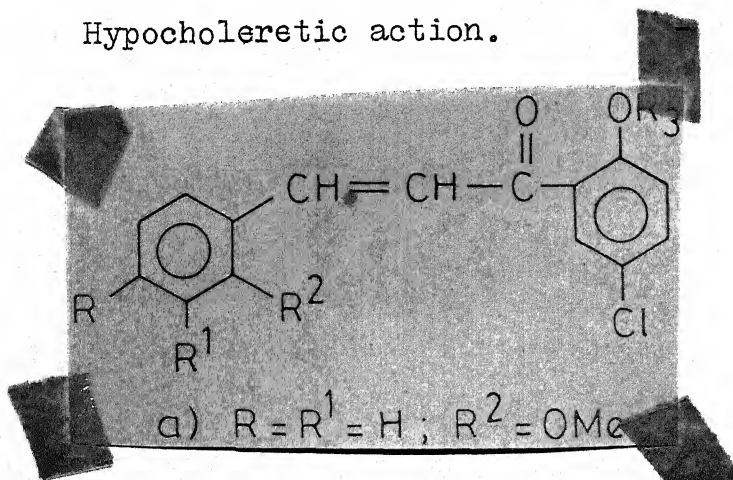
Flavonol  
derived from  
2'-hydroxy-2,  
4',5',6,6'-  
pentamethoxy  
chalcone

Potential antitumor compound. -

92

### Choleretic/Hypocholeteretic Activity

- a) 4,4'-  
Dihydroxy-  
2'-methoxy  
chalcone      These compounds exhibit a      Rats      93  
greater activity than the  
currently used choleretics.
- b) 2',4,4'-  
Trimethoxy-  
chalcone  
(vesidryl)      61
- a) 3'-Nitro-  
4'-hydroxy-  
2-methoxy  
chalcone      Possesse choleretic      Rats      6  
effect in vivo. Compound  
(a) has the highest  
choleretic effect.
- b) 3'-Nitro-  
4'-hydroxy-  
2,3-dime-  
thoxy  
chalcone
- c) 3'-Nitro-  
4'-hydroxy-  
2,5-dime-  
thoxy  
chalcone
- 2',4',6'-  
Trihydroxy      Hypocholeteretic action.      79



$R_3=2$ -Morphinoethyl sulphate 94

b)  $R=R_1=R_2=H$ ;  
 $R_2=CH_2COOH$

Pyridine analogue of chalcone      Choleric property.      -      95

### Spasmolytic Activity

Chalcone; 2- (and 2')-Hydroxy chalcones; 2,4-dihydroxy-chalcone; 2,2'-dihydroxy-chalcone; 2,4,4'-trihydroxy chalcone and 2,2',4-trihydroxy-chalcone      Exhibit spasmolytic action. Isolated bowels and stomach of rats      96

Salts of N-substituted 4'-aminoalkoxy-2',4-dihydroxy chalcones      These compounds possess relatively high muscular spasmolytic and low neuro-spasmolytic properties.      Mouse      97

Reduced benzofuran chalcone derivatives      Compound with  $R=4-OH$ , and  $NR^2$ =piperidine has the highest spasmolytic activity.      -      83

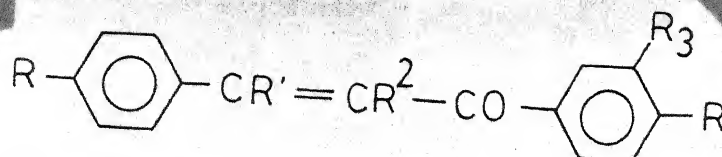
Bis(Phenyl-  
alkyl) amines-  
the catalytic  
reduction  
products of  
chalcone oxime

Potential spasmolytic  
compounds.

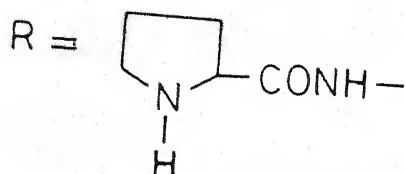
98

Licurzid  
(chalcone)

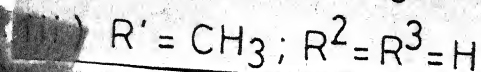
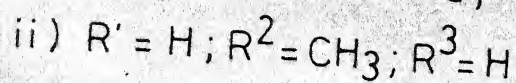
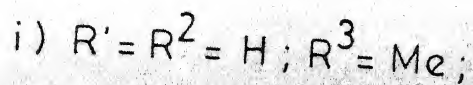
99



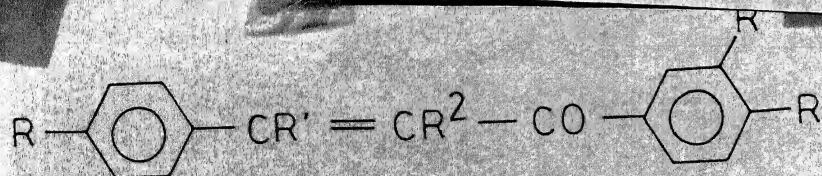
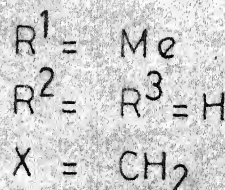
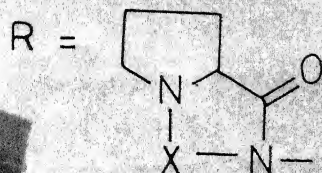
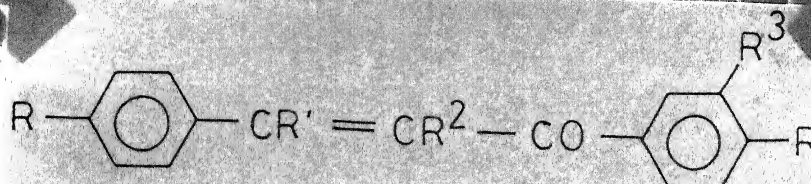
Antispasmodi



Active

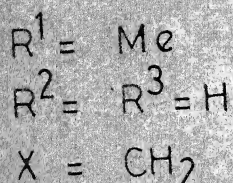
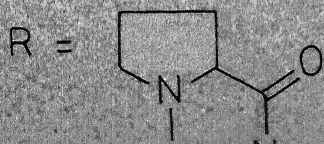


100, 101



Active

102



Anti-inflammatory Activity

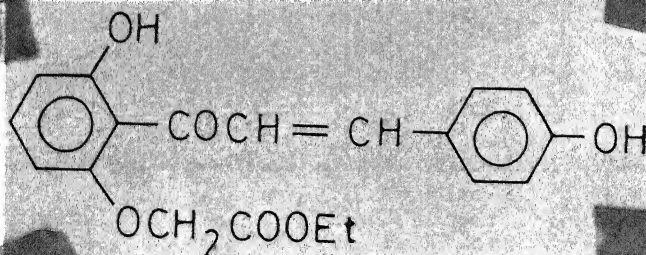
Substituted chalcones	-	-	49
5-Cinnamoyl salicylic acid	-	-	24

Analgesic and Sedative Action

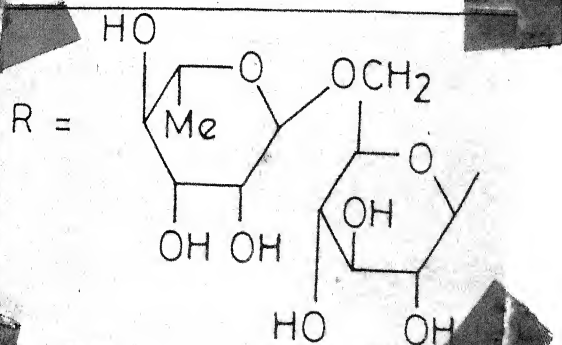
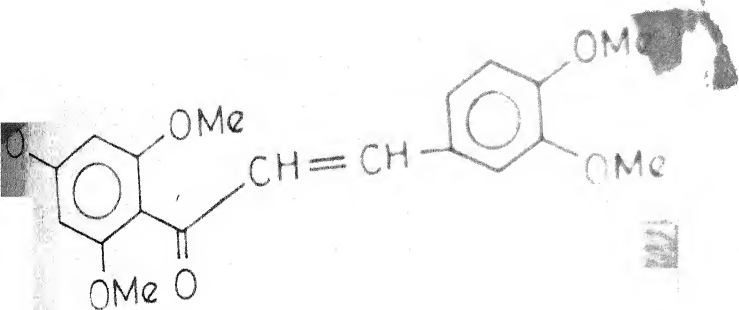
Substituted chalcones	-	-	49
5-(4-chloro- cinnamoyl)- salicylic acid	Analgesic effect is similar to that of aspirin.	-	24

Antithrombic Activity

Substituted chalcones	-	-	49
Flavone derived from the following chalcone:	Potential antithrombic active compound.	-	103

Capillary Fragility

Various chalcones	Restore capillary resistance.	Guinea pigs	104
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Decreases capillary  
fragility and also effects  
venous circulation.

-

105

Chalcone and  
hesperidin  
methyl  
chalcone

These compounds effect the Mice  
fragility of capillaries  
present in the inner  
surface of the abdominal  
skin.

106

### Vasodilatory Activity

- a)  $\omega$ -Aminoalkoxy  
chalcones  
and acid  
addition  
salts
- Coronary vasodilatory  
properties are associated  
with these compounds.
- b) Reduced  
benzofuran  
chalcone  
derivatives

-

82-84,  
107

Mecinarone (a benzofuranic chalcone)	Vasodilatory activity (on the peripheral and cerebral circulation).	Experimental animals	108
Pyridine analogues of chalcone	Coronary vasodilative properties.	-	95

### Estrogenic Activity

2'-Hydroxy(and 2'-chloro)-3,4-methylene dioxy-4'-fluoro-chalcones; and 2'-chloro-4,4'-difluoro-chalcone	These compounds produced uterotropic effect, decreased the weight and size of the testes and seminal vesicles and inhibited implantation in the mouse.	Mice	109
4,2',4'-Tri-methoxychalcone epoxide and 4-methoxy-2',4'-dibenzoyloxy chalcone epoxide	Estrogenic activity(?)	Rats	110

### Anesthetic Activity

Pyrazole derived from 4-dimethyl amino chalcone	It has some local anesthetic activity.	-	111
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### Anticoagulating Effect

2',4',6'-Trihydroxy chalcone	Anticoagulating properties.	-	79
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Anticonvulsant/Narcotic Potentiation Activity

3,4-Methylene dioxychalcone	It has proved effective as anticonvulsant; and also shows narcotic potentiation activity.	-	112
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Therapeutic Activity

Cyanomethyl- chalcones	These compounds are claimed as valuable medicinal agents for cardiovascular diseases and endocrine dysfunctions.	-	113
Hesperidin methyl carboxy chalcone	It exerts therapeutic action in the treatment of chronic diseases of the eye and kidney including rheumatoid diseases like bursitis and osteoarthritis.	-	114
Hesperidin methyl chalcone	The compound, when incor- porated in diet (0.2%), shows an inhibitory effect on the incidence of dental caries.	Cotton rats	115

Antiangiotensin/Antiarrhythmic/Diuretic Activity

Reduced benzofuran chalcone derivative(cf. spasmolytic activity)	These compounds possess antiangiotensin, antiarrhy- thmic and diuretic activity.	-	85
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### Miscellaneous Biological Activities

Chalcone, 2-hydroxy chalcone; 2',3-dihydroxy chalcone and hesperidin chalcone      These compounds are able to protect adreline from destruction (vitro).      Isolated strip of intestine      116

Dialkylamino alkoxy derivative of chalcone      Potential adrenergic blocking agents.      -      117

Aminoaza chalcones      Adrenal cortex inhibitors      Rats      118

Azachalcones:      Suprarenal gland inhibitors      Rat      122

enone type.

ese compounds

tive than

R=2-pyridyl;

R=ph; 4-NH-(Me)C<sub>6</sub>H<sub>4</sub> or

R=4-N(Me)<sub>2</sub>-C<sub>6</sub>H<sub>4</sub>

Substituted chalcones      The most potent compound in respect of pharmacological activity is 2(2-dimethylaminoethoxy) chalcone, but it does not compare with the available therapeutic agents in specificity, potency and duration of action.      -      119

Licurzid (chalcone)	<p>a) Reduces stomach motility.</p> <p>b) Inhibits evacuation of water from stomach to deudenum.</p> <p>c) Inhibits development of exudative processes in the inflammation and prevents development of neurogenic and buta-dione stomach ulcers.</p>	Rats and Mice	99
2-[2-dimethyl aminoethoxy)- 3',4',5'- trimethoxy] chalcone hydrochloride	<p>a) This compound is an effective and long active depressor agent.</p> <p>b) There is an electrolytic alteration between blood vascular smooth muscles following treatment with the chalcone.</p>	Dogs and rats	120
Sulphur containing derivative of chalcone, viz. $\text{O} \text{COCH}_2 \text{S}-\text{C}_6\text{H}_4 \text{Cl}$ , obtained by the interaction of the chalcone epoxide with thiol	Biological activity	-	121

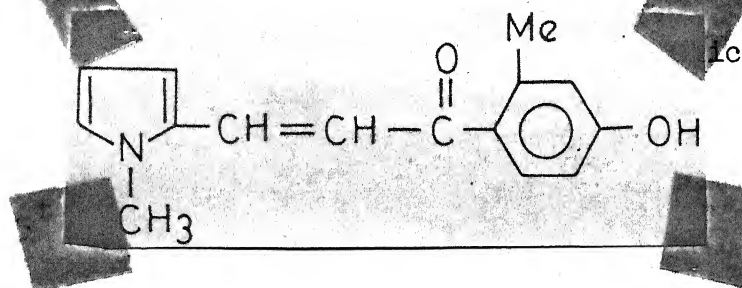
Action on Spermatocytic Chromosomes

2',4'- Dihydroxy chalcone	The rejoining of broken ends of chromosomes and chromatids is accelerated by the addition of chalcone.	Grasshopper	123
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Decrease in the Incidence of Blood Spots in Chicken Eggs

a) 3-Pyrrole- 2-aldehyde chalcone	Active	Chicken eggs	124
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b)		Chicken eggs	125
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Plant Growth Inhibiting Activity

3,2',4'- trihydroxy-4- methoxy- dihydro- chalcone	Inhibitory effect on the growth of plant-triticales	Triticale <sup>a</sup>	126
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CHAPTER - 18.1

## CHALCONE EPOXIDES

## Synthesis

- i) By Darzens Condensation..... 345
- ii) Oxidation of Chalcone..... 345

## Reactions

- With Toluene..... 345
- Thiophenols and Thioalcohols..... 346
- Amines..... 346
- Hydroxylamine..... 346
- Hydrazines..... 347
- o-phenylenediamine..... 347
- Reducing Agents..... 347

## With Acids

- Hydrochloric Acid..... 348
- Dry HCl in Ether..... 349
- Dilute Sulphuric Acid in Methanol..... 351
- Ethanol-HCl..... 352
- Boron Trifluoride Etherate..... 353

## With Alkalis..... 354

- Stannous Chloride..... 355

## Miscellaneous Properties..... 355

## Conformation..... 356

## References..... 357

Synthesis:

Epoxy derivatives of chalcones, and their heterocyclic analogues, viz., thienyl, seleno<sup>ie</sup>phenyl and pyridyl, have been prepared by the following methods<sup>1</sup>:

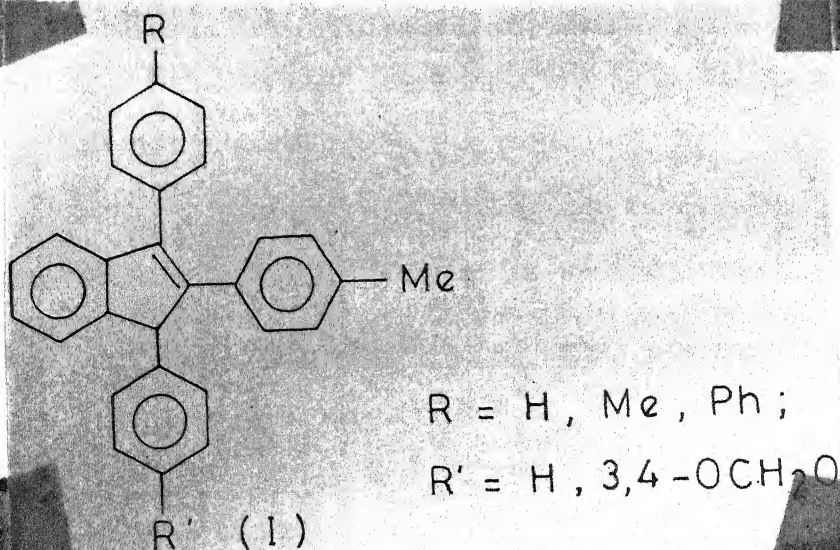
- i) By Darzens condensation of aldehydes with haloacyl compounds.
- ii) By the oxidation of chalcones and their heterocyclic analogues with alkaline hydrogen peroxide. This method has been exploited for the synthesis of the epoxides derived from vinyl-<sup>2</sup> and o-methoxychalcones<sup>3</sup>.

Reactions:

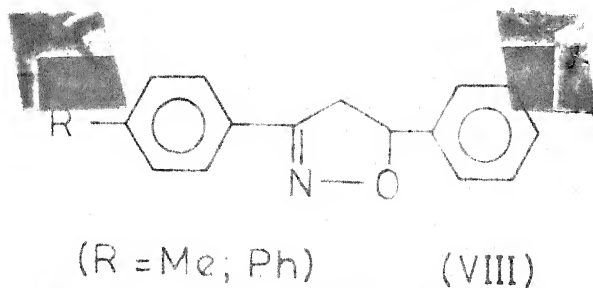
A review on the reactions of substituted chalcone epoxides has been published.<sup>4</sup>

With Toluene:

Friedel-Craft alkylation of epoxychalcones with toluene, in presence of anhydrous  $\text{AlCl}_3$ , is reported<sup>5</sup> to yield indenenes (I).

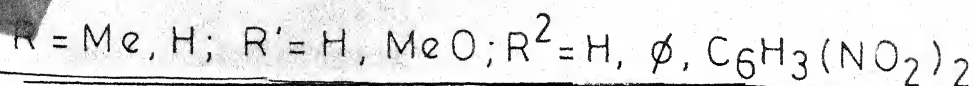
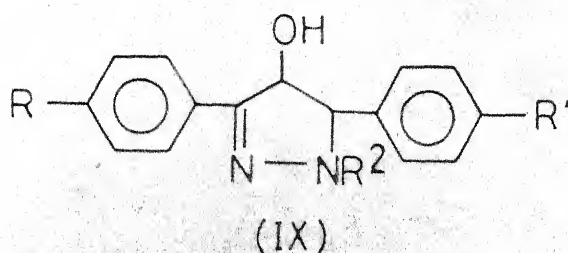
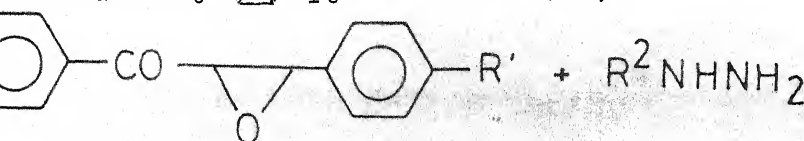






With Hydrazines:

Substituted chalcone epoxides are reported to react with hydrazine<sup>5,6,9-11</sup> or its substituted derivatives to yield 3,5-diaryl-4-hydroxy- $\Delta^2$ -pyrazolines (IX):

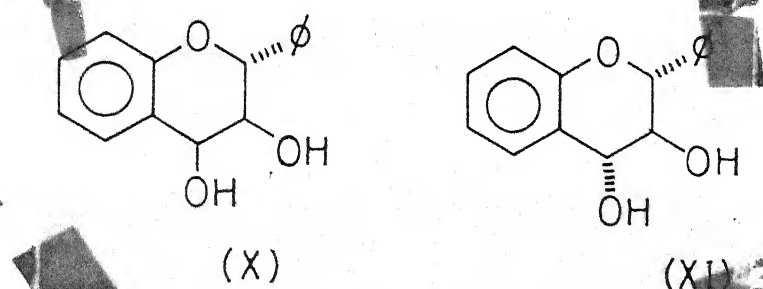


2-Phenyl-benzimidazole (10%) has been secured<sup>12</sup> by the reaction of o-phenylenediamine with trans chalcone epoxide.

With Reducing Agents:

Trans-chalcone epoxide on reduction with lithium aluminium hydride<sup>13</sup> gives the mixture of erythro-1,3-diphenyl-1,2-propandiol

and (+) 1,3-diphenyl-1,2-propandiol. The same products are produced when trans-chalcone <sup>epoxide</sup> is catalytically hydrogenated over  $\text{PtO}_2$ .<sup>13</sup> 2'-benzyloxychalcone epoxide on treatment with  $\text{KBH}_4$  or  $\text{LiAlH}_4\text{-AlCl}_3$  (1:7) is reported<sup>14</sup> to yield trans-2,3-cis-3,5-flavandiol (X). However, the epoxide of 2'-methoxymethoxy chalcone under these conditions, gives a mixture of two isomeric diols (X) and (XI), the former predominating:



Chalcone and 1,4-dibenzoyl-2,3-diphenylbutane are produced when chalcone epoxide is reduced by chromous chloride.<sup>15</sup>

## Acids

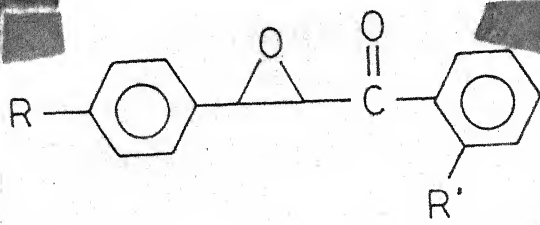
### With HCl:

The kinetics and mechanism of the cyclisation of 2'-hydroxy-chalcone epoxide to the 3-hydroxyflavanone in water has been investigated.<sup>16</sup> The treatment of 2'-(4-methoxybenzyl)-4,4'-dimethoxychalcone epoxide with HCl in acetic acid is reported<sup>17</sup> to give trans 3-hydroxy-7,4'-dimethoxyflavanone. On the other hand, trans 4'-methoxychalcone epoxide on treatment with HCl furnishes the corresponding chlorohydrins.<sup>18</sup> The chlorohydrins have been found by N.M.R. Spectroscopy to correspond to threo and erythro configurations<sup>18</sup> respectively. Under the same conditions,

3-nitrochalcone/<sup>epoxide</sup>, however, yields only one isomer,<sup>18</sup> viz., erythro. Several chlorohydrins (erythro and threo) have been synthesized.<sup>19,2</sup> The reaction of hydrazine with several chlorohydrins have been studied.<sup>10</sup>

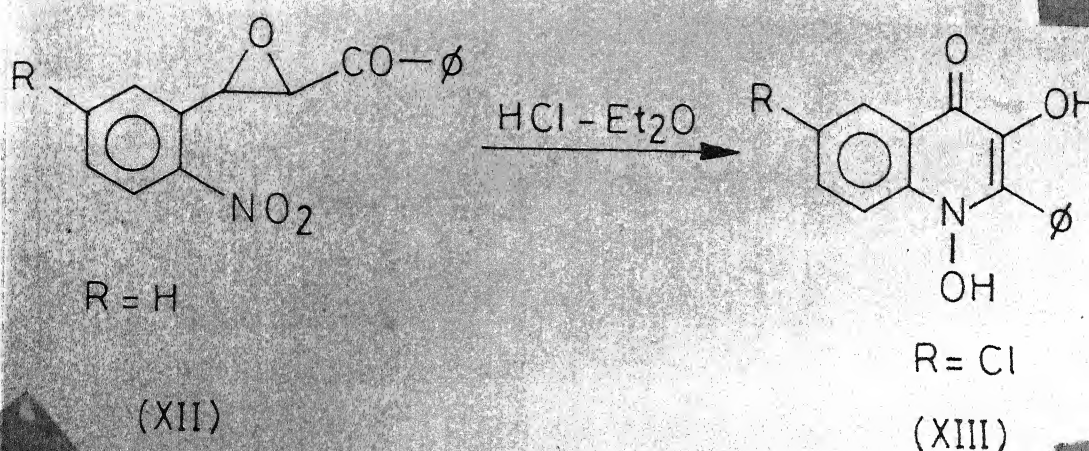
With Dry HCl in Ether:

The treatment of 4'-methylchalcone<sup>epoxide</sup> with dry HCl in ethereal solution yields 1-(p-tolyl)-2-hydroxy-3-chloro-3-phenylpropan-1-one.<sup>21</sup> The effect of various functional groups (R and R') on the oxirane ring opening by HCl or BF<sub>3</sub> has been studied.<sup>22</sup>

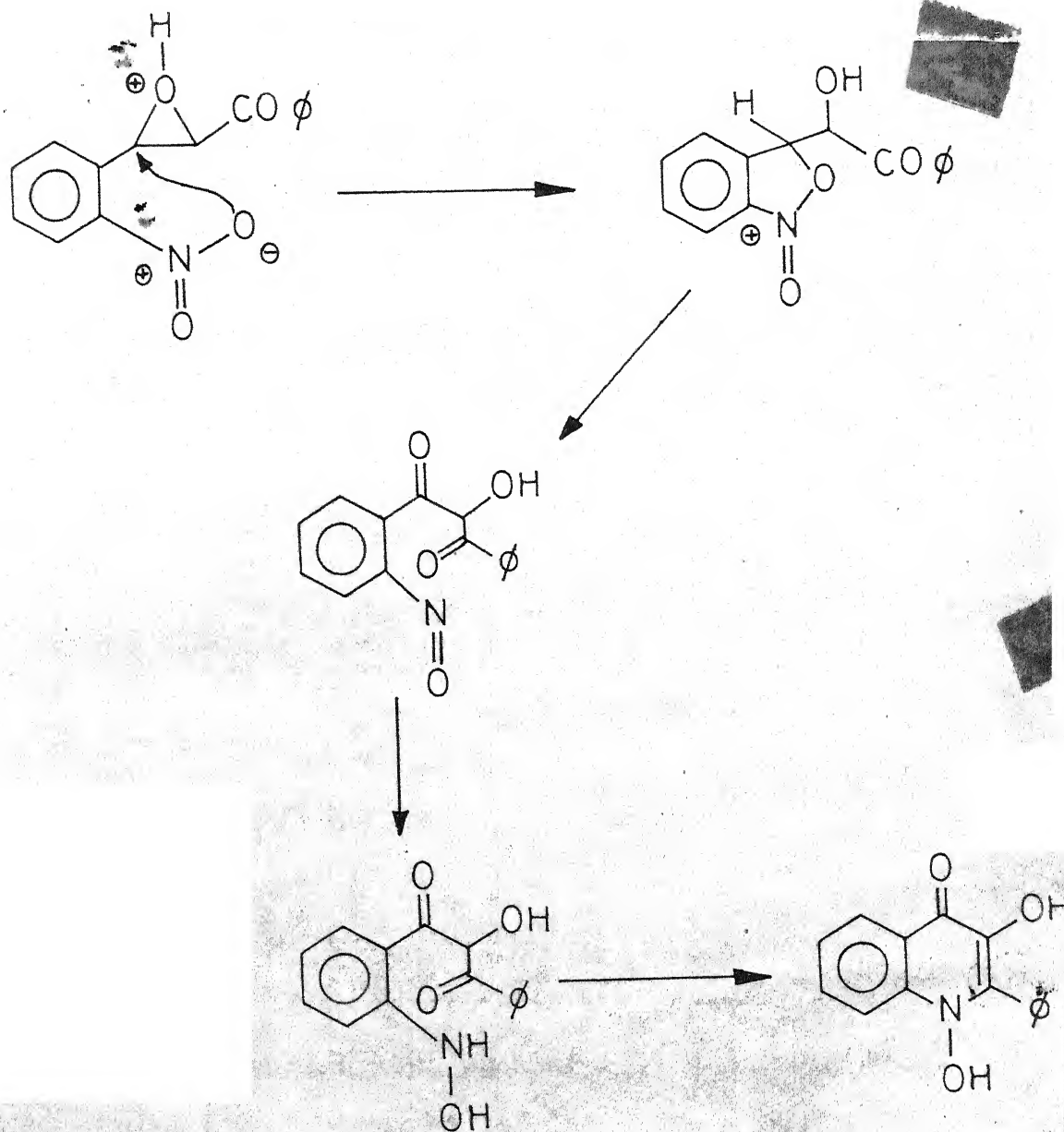


R, R' = Me<sub>2</sub>N, H; MeO,  $\phi$ CH<sub>2</sub>O; Br, H; NO<sub>2</sub>,  $\phi$ CH<sub>2</sub>O

2-Nitrochalcone epoxide (XII) reacts with ethereal hydrogen chloride to yield 6-chlor-1,3-dihydroxy-2-phenylquinolin-4-(1H)-one<sup>23</sup> (XIII). The same reactants in the presence of quinol, gives the unchlorinated product<sup>23</sup> (XIII, R = H).



The mechanism of this reaction can be rationalized as follows<sup>23</sup>.



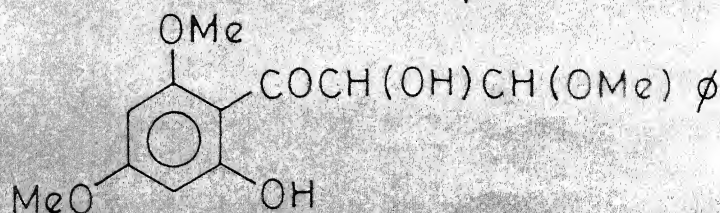
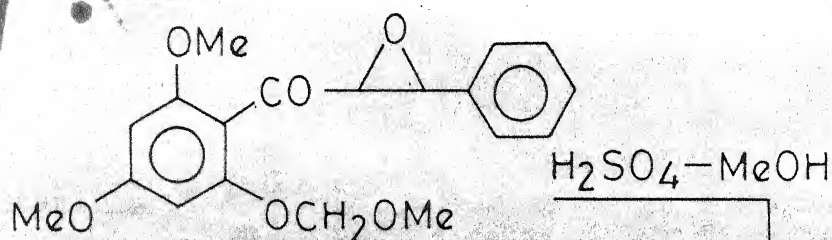
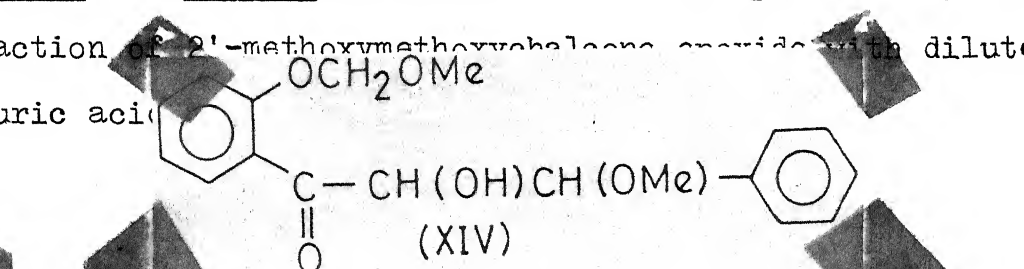
resulting in the formation of nitrosophenyl ketone. The nitroso group can be reduced to hydroxylamine group before cyclisation can occur. Quinol serves this purpose, and the unchlorinated product (XIII, R = H) is thereby obtained. However, hydrogen chloride acting alone can cause reduction by insertion (at position 6) of chloride ion into the original nitrophenyl nucleus (XIII; R = Cl).



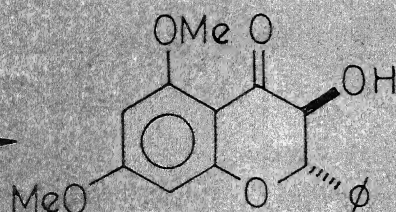
Substituted 2'-benzyloxychalcone epoxides react with HCl saturated ether to yield either chlorohydrins or flavon-3-ol (or both) depending upon the value of  $\sigma$  (the substitution constant<sup>24</sup>) of the substituent in ring A. Treatment of the epoxide of 2'-benzyloxychalcone analogue-containing condensed rings and or heterocyclic ring system, with HCl-Et<sub>2</sub>O yield the chlorohydrins.<sup>24</sup>

With Dilute Sulphuric Acid in Methanol<sup>25</sup>:

Threo and erythro mixtures of (XIV) are produced by the interaction of 2'-methoxymethoxychalcone epoxide with dilute sulphuric acid



Conc. H<sub>2</sub>SO<sub>4</sub>





Racemic 4',5,7-tri-O-methylaromadendrin and 3',4',5,7-tetra-O-methyl taxifolin have been prepared<sup>26</sup> in an analogous manner.

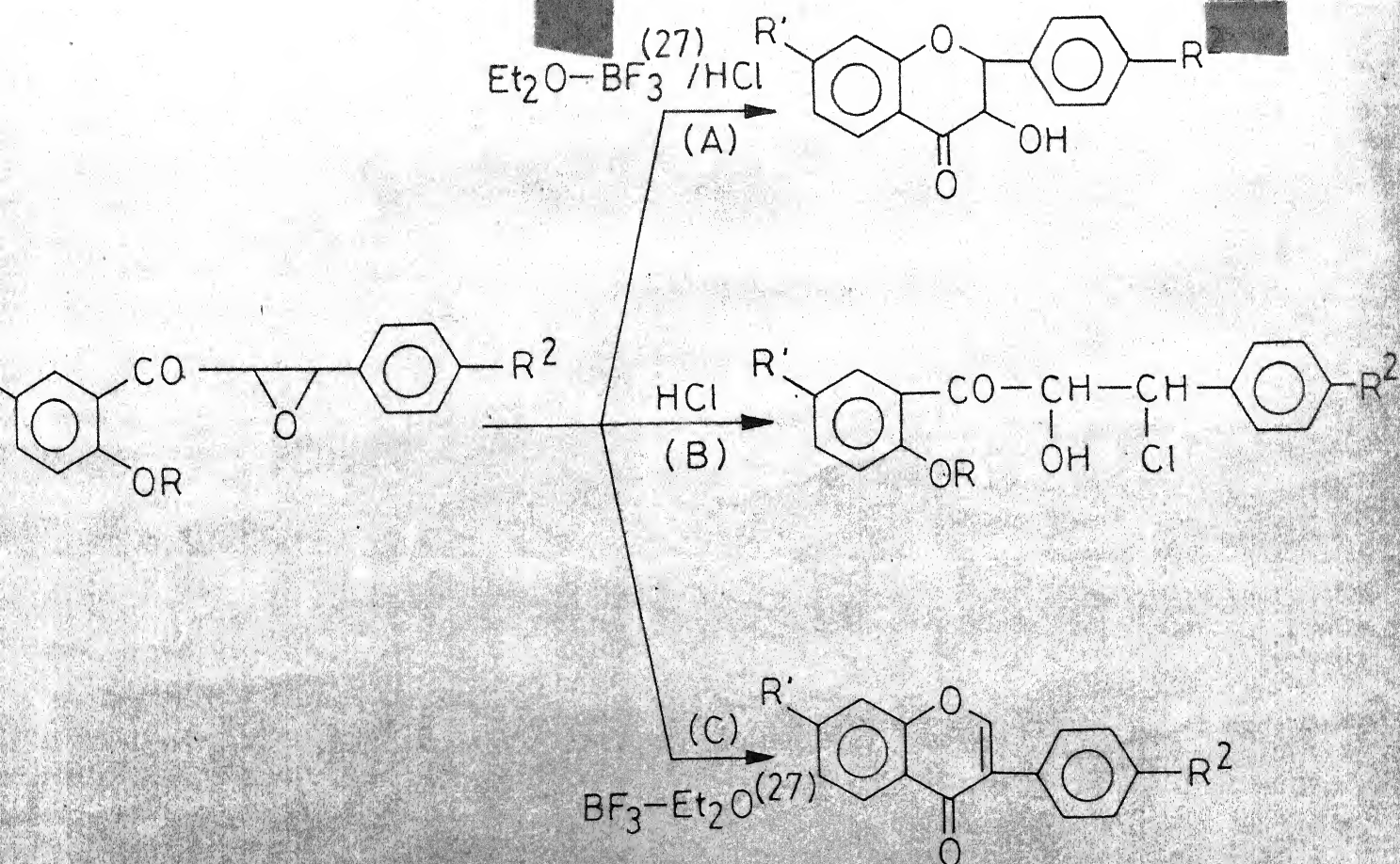
With Ethanol-HCl:

2'-Benzyloxychalcone epoxide and 2'-benzyloxy-4-methoxy-chalcone epoxide exhibit a contrast in their behaviour towards ethanolic-HCl. Thus, in the presence of ethanol-HCl, the former epoxide undergoes cyclisation to give 3-hydroxyflavanone.<sup>27</sup> In this example the benzyl group is split off earlier than the cleavage of the oxirane ring and the 2'-phenolate ion formed attacks the  $\beta$ -carbon atom,<sup>27,28</sup> and thus effects cyclisation to 3-hydroxyflavanone. On the other hand 2'-benzyloxy-4-methoxy-chalcone epoxide, reacts with ethanol to give 2'-benzyloxy-4-

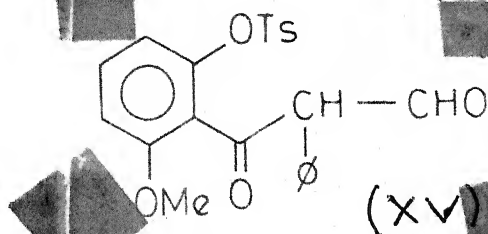
methoxy- $\alpha$ -hydroxy- $\beta$ -ethoxy-dihydrochalcone (XIV-A). Treatment of (XIV-A) with HCl results in the formation of 1-(2-benzyloxyphenyl)-2-hydroxy-3-chloro-3(p-methoxyphenyl)-propan-1-one<sup>27</sup> (XIV-B)

With Boron Trifluoride Etherate:

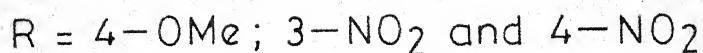
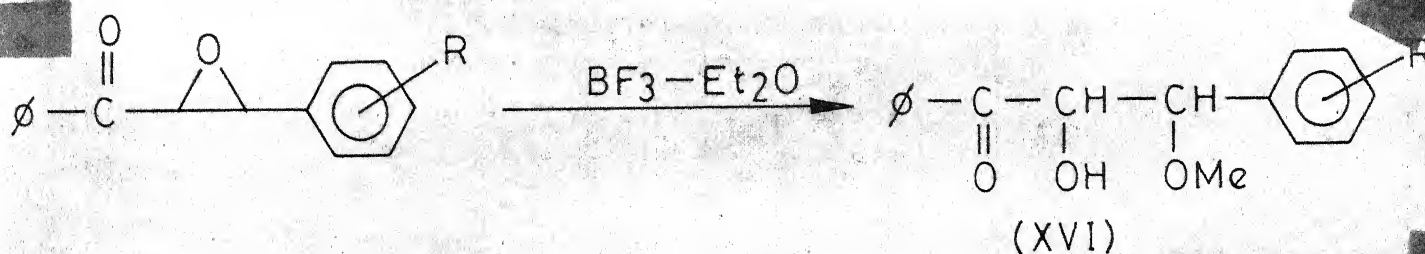
5-substituted chalcone epoxides react with  $\text{BF}_3\text{-Et}_2\text{O}$  (including HCl) to give different products viz., flavan<sup>an</sup>ol,<sup>19</sup> isoflavone<sup>19</sup> or chlorohydrin<sup>19,20</sup> depending upon the Hammett value<sup>19</sup> of 5'-substituent



2'-Tosylchalcone epoxide<sup>oxy</sup> yields<sup>yields</sup> on treatment with  $\text{BF}_3\text{-Et}_2\text{O}$ , a mixture of 3-hydroxyflavanone and flavonol,<sup>29</sup> on the other hand, 6'-methoxy-2'-tosylchalcone epoxide<sup>oxy</sup> yields the ketoaldehyde (XV):



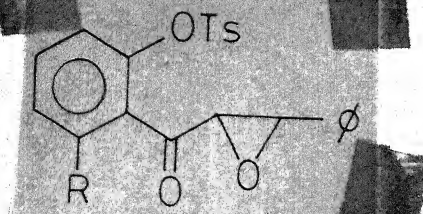
The addition of methanol to chalcone epoxide is reported<sup>30</sup> to take place according to the equation:



addition product.

#### With Alkalis:

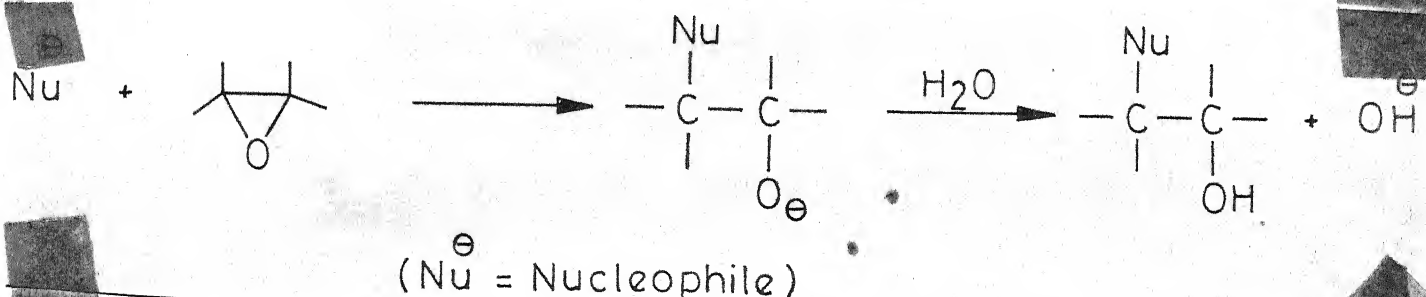
2'-Tosylchalcone epoxide (XVII;  $\text{R} = \text{H}$ ) with caustic alkali in methanol is reported<sup>29</sup> to give flavanol, while on the other hand 2'-tosyl-6'-methoxychalcone epoxide (XVII;  $\text{R} = \text{OCH}_3$ ) at room temperature or in refluxing solvent, yields 4-methoxyaurone:



With Stannous Chloride<sup>31</sup>:

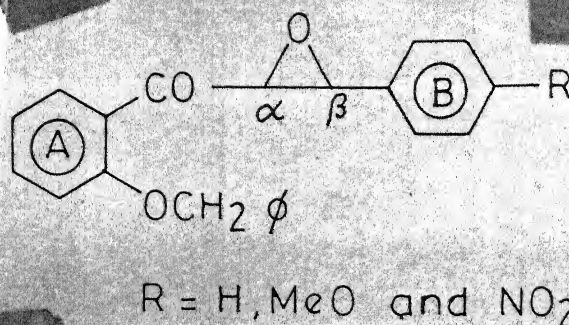
2-Methoxychalcone epoxide (XVIII) is reported to yield 1-(2-methoxybenzoyl)-2-phenyl-ethylene chlorohydrin (XIX) when the benzene solution of the former is reacted with stannous chloride. XIX is transformed by heating (140-150°) into an  $\alpha$ -diketone or into a diol by hydrogenation over Pd-C catalyst. Under the same conditions, XVIII gives a ketoalcohol.

Based on kinetic experiments the following mechanism has been reported<sup>32</sup> for the ring opening of chalcone epoxides:



#### Miscellaneous Properties:

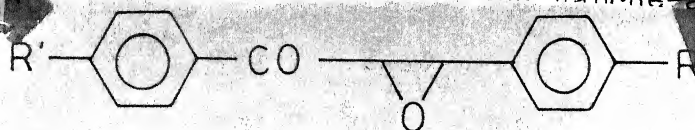
Quantum chemical methods<sup>28,33</sup> indicate that the para substituent (B) affected the electron density at the  $\beta$ -carbon atom.



On the basis of infrared spectroscopic data it has been demonstrated<sup>34</sup> that oxirane ring of chalcone epoxides exert an electron withdrawing influence on the carbonyl group and thereby decrease its basicity.

### Conformation:

The conformation of chalcone epoxides has been derived both from spectroscopic studies<sup>34,35</sup> as well as from dipole moment measurements.<sup>37</sup> Thus a conjugated cisoid conformation, in the solid state as well as in  $\text{CCl}_4$  solution has been reported for 2'-benzyloxychalcone epoxide.<sup>35</sup> The gauche conformation<sup>36</sup> is adopted in solid phase by the epoxides of chalcone, 4,4'-dimethoxychalcone and 4,4'-dichlorochalcone, which, however, changes in solution (chloroform/carbon tetrachloride) to a gauche-cis mixture.<sup>36</sup> Based on the dipole moment studies the following chalcone epoxides are reported<sup>37</sup> to exist probably as an equilibrium mixture of gauche-cis and gauche-anti conformers.



$R = R' = \text{H}; \text{MeO}; \text{and Cl}$

The following chalcone epoxides are reported<sup>37</sup> to exist in solution,



$R, R' = \text{H, H}; \text{H, OMe}; \text{H, Br}; \text{Br, H};$   
 $\text{NO}_2, \text{H and H, NO}_2$

as equilibrium mixtures of polar gauche and anti conformers.

The absolute configuration of chalcone epoxide, based on chemical correlation, has appeared in literature.<sup>39</sup>

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CHAPTER - 18.2CHALCONE  $\alpha, \beta$  -DIBROMIDES

## Reactions:

Synthesis of Flavones.....	362
Aurones.....	365
Benzoylcoumarone.....	368
Flavonol and Dihydroflavonol.....	368
Flavanones.....	369
Tetralones.....	370
Benzalacetone.....	371
Aziridines.....	371

## Miscellaneous Reactions:

Reaction with Halogens.....	372
Alcohols.....	372
Potassium Cyanide.....	372
Hydrazine Hydrate.....	372
Sodium Azide.....	373

Cleavage of $\alpha$ -bromochalcone with HBr and Oxygen.....	373
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References.....	373
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Reactions:

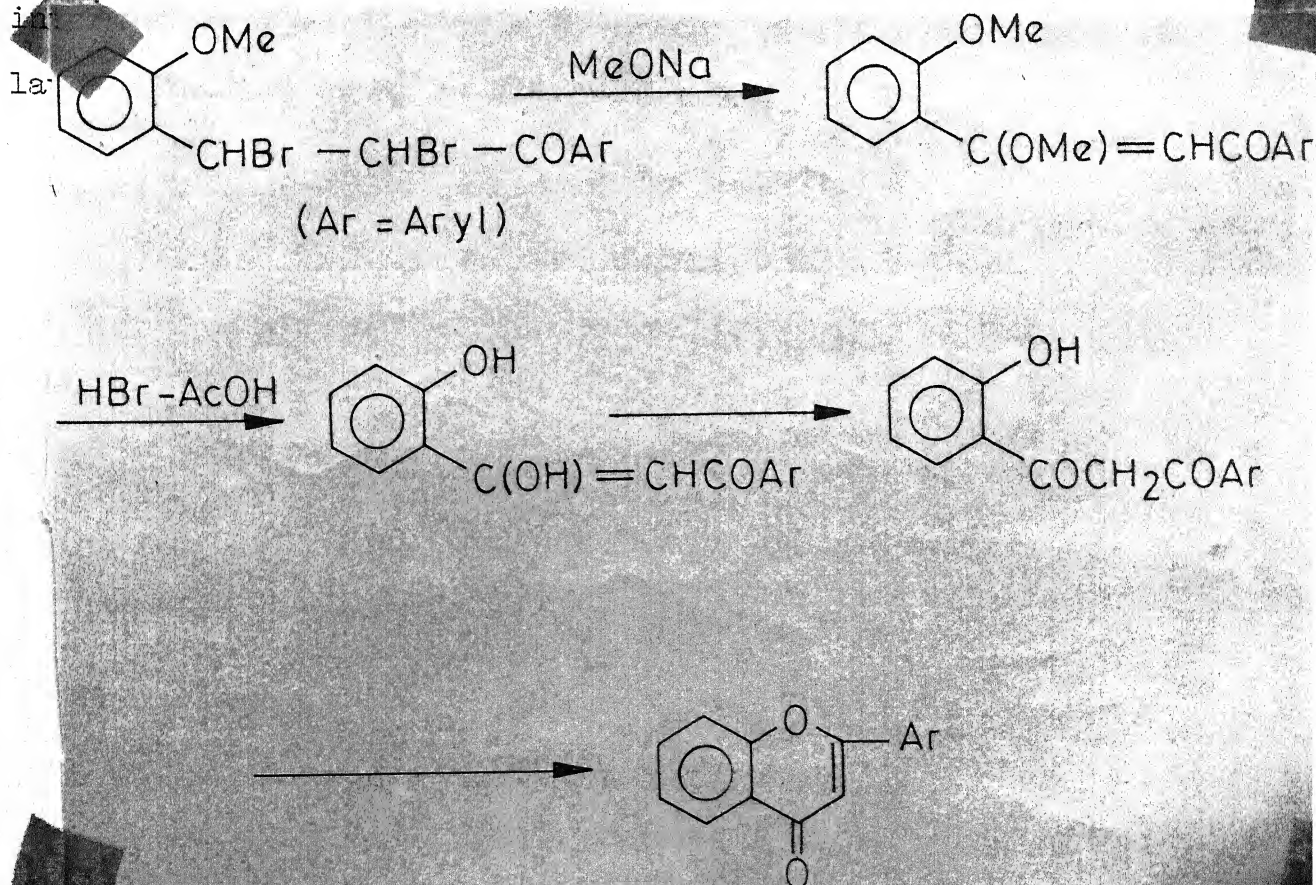
The reaction of substituted chalcone dibromides have been studied in considerable detail. Thus under varied experimental conditions the following types of compounds have been obtained

from chalcone dibromides viz., flavones,<sup>1-23</sup> flavonol,<sup>24,28</sup> flavanones,<sup>29,30</sup> aurones<sup>2,7,8,10,11,22,24-26</sup> benzoylcoumarones,<sup>12</sup>  $\alpha$ -bromochalcones,<sup>22,31</sup> tetralones,<sup>33</sup> aziridines<sup>5,23</sup> etc.

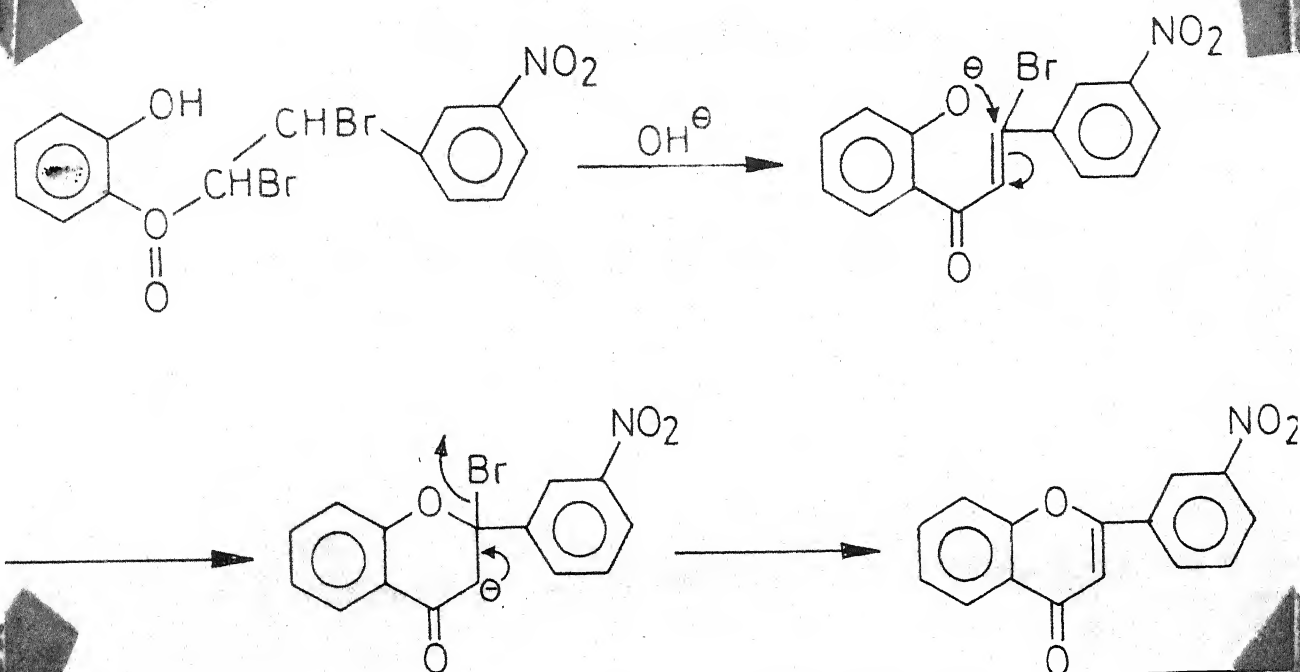
### Synthesis of Flavones<sup>1-23</sup>:

Flavones have been secured either by the pyrolysis<sup>3,9</sup> of *o*-hydroxy (or *o*-acetoxy) chalcone  $\alpha, \beta$ -dibromides or by their reaction with alcoholic alkali,<sup>2,5-13</sup> sodium methoxide,<sup>4</sup> pyridine<sup>1,15-21</sup> or potassium cyanide.<sup>3,22</sup> The latter reaction has been utilized<sup>3</sup> for the synthesis of naturally occurring flavones, containing a phloroglucinol nucleus, viz., chrysin, apigenin and luteolin.

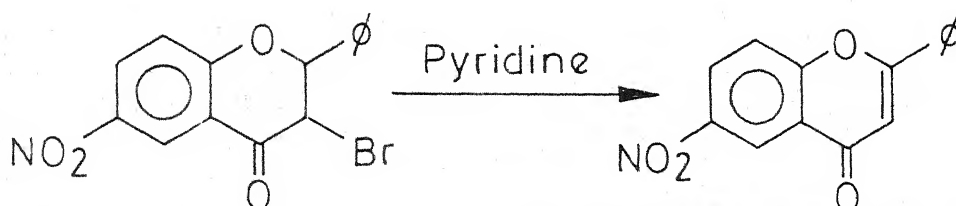
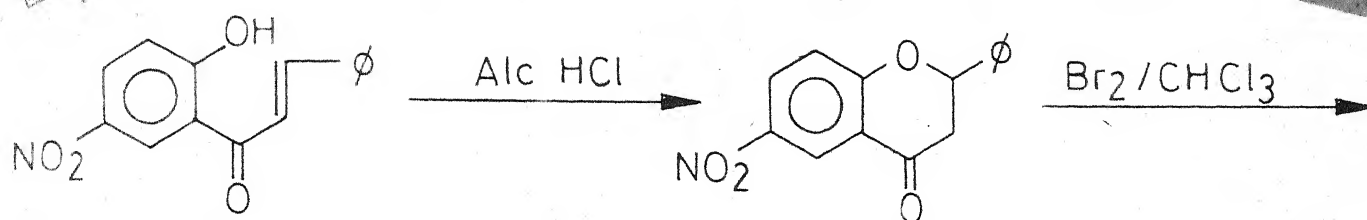
In the conversion of *o*-substituted chalcone dibromide into the corresponding flavone, under the influence of a base, the



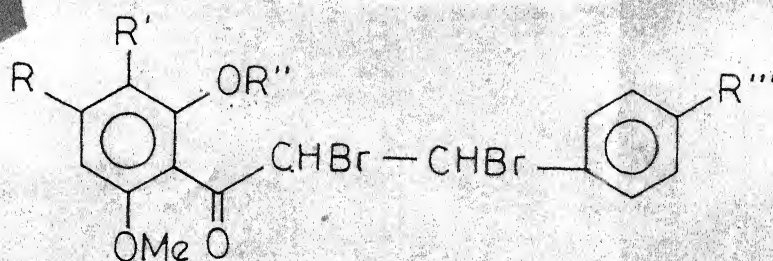
The formation of flavone from 2'-hydroxy-3-nitrochalcone dibromide has been rationalized<sup>8</sup> in the following way:



In this case pyridine behaves like an alkali and brings about dehydrobromination and cyclisation. Nuclear substitution in this case is not feasible since the probable position of entry of the bromine is already occupied. Utilising this reaction some substituted flavones have been synthesized. 8-Nitro-7-hydroxyflavone has been prepared<sup>15</sup> in the aforesaid manner. The isomeric compound viz., 5-hydroxy-6-nitroflavone, however, can be prepared<sup>15</sup> as follows:



In the synthesis of flavones from chalcone dibromides and ethanolic alkali, it has been demonstrated<sup>13</sup> that steric effects do play an important role. Thus flavone derived from chalcone (Ia) is obtained in 89% yield, while the flavone from chalcone (Ib) is secured in a relatively low yield (46%).

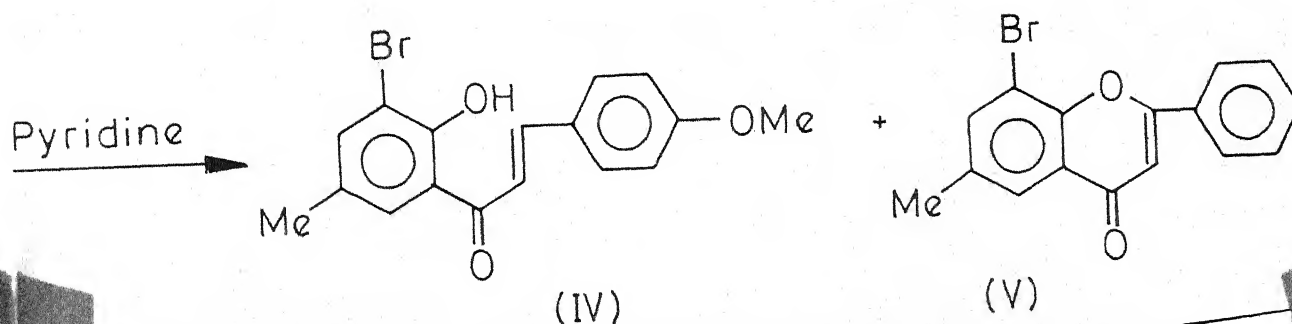
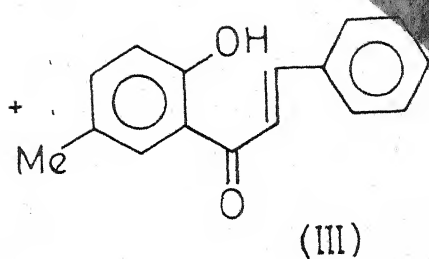
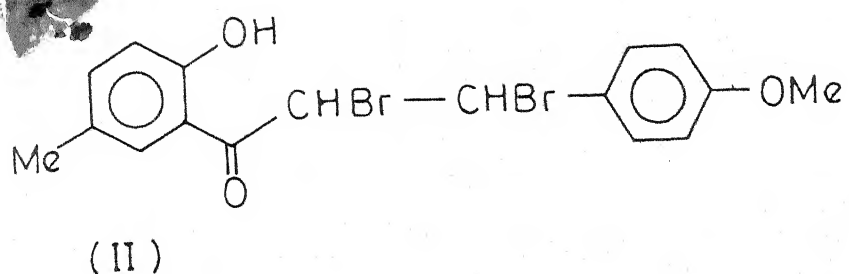


(Ia)  $R = R' = R'' = H$ ;  $R''' = Ac$

(Ib)  $R = R'' = H$ ;  $R' = Br$ ;  $R''' = Ac$

In this reaction, aurone is also formed, but in smaller amounts.<sup>13</sup>

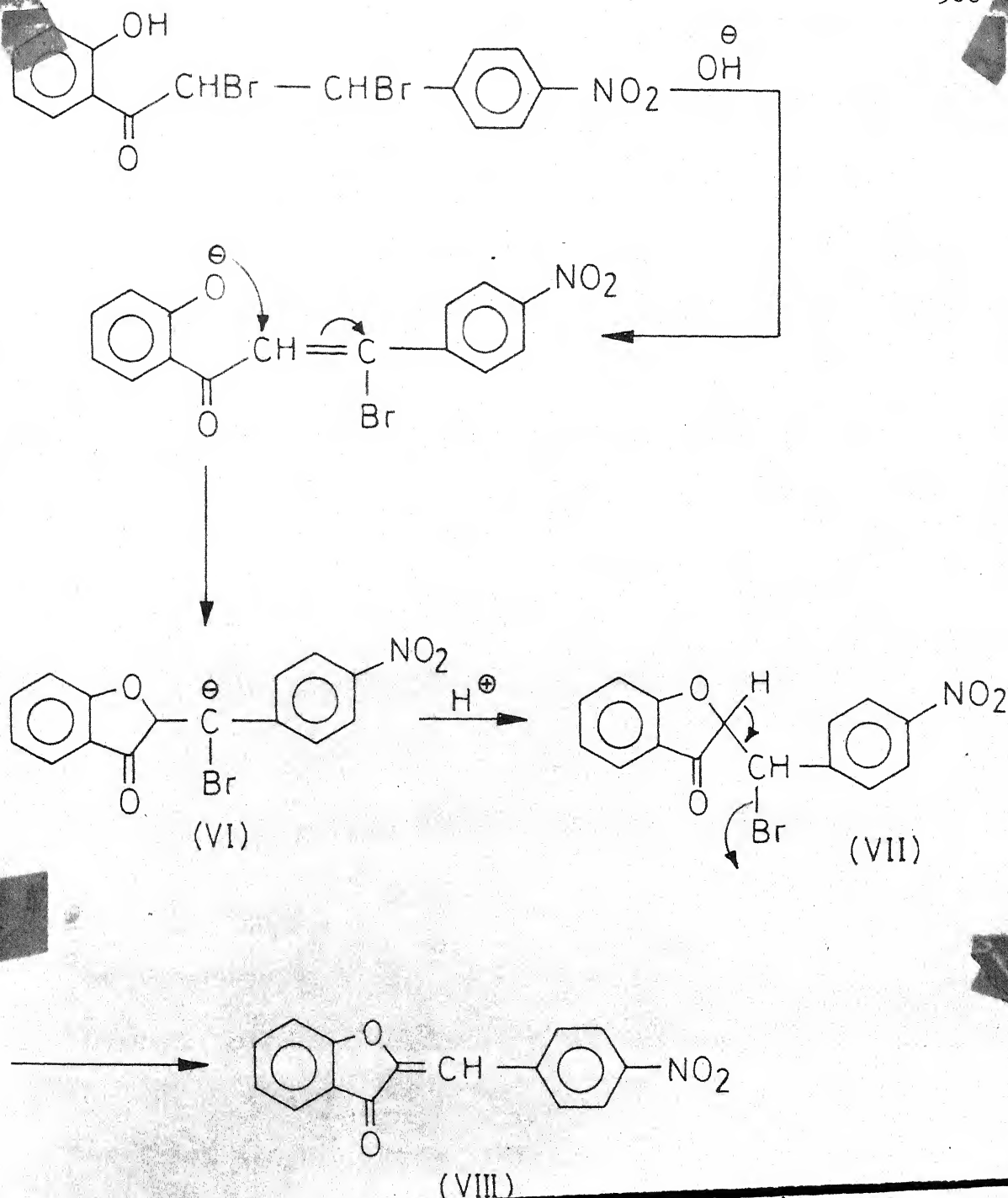
A mixture of 2'-hydroxy-5'-methyl-4-methoxychalcone bromide (II) and 2'-hydroxy-5'-methylchalcone (III) is reported<sup>23</sup> to react in the presence of pyridine leading to the formation of cross brominated products (IV and V):



~~mechanism,~~  
 followed by oxidative cyclisation.

Aurones<sup>2,7,8,10,11,22,24,25,26</sup>:

2'-Hydroxy-4-nitrochalcone dibromide undergoes ring cyclisation under the influence of alkali, to yield the corresponding aurone. The following mechanism has been advanced<sup>8</sup> for this reaction:



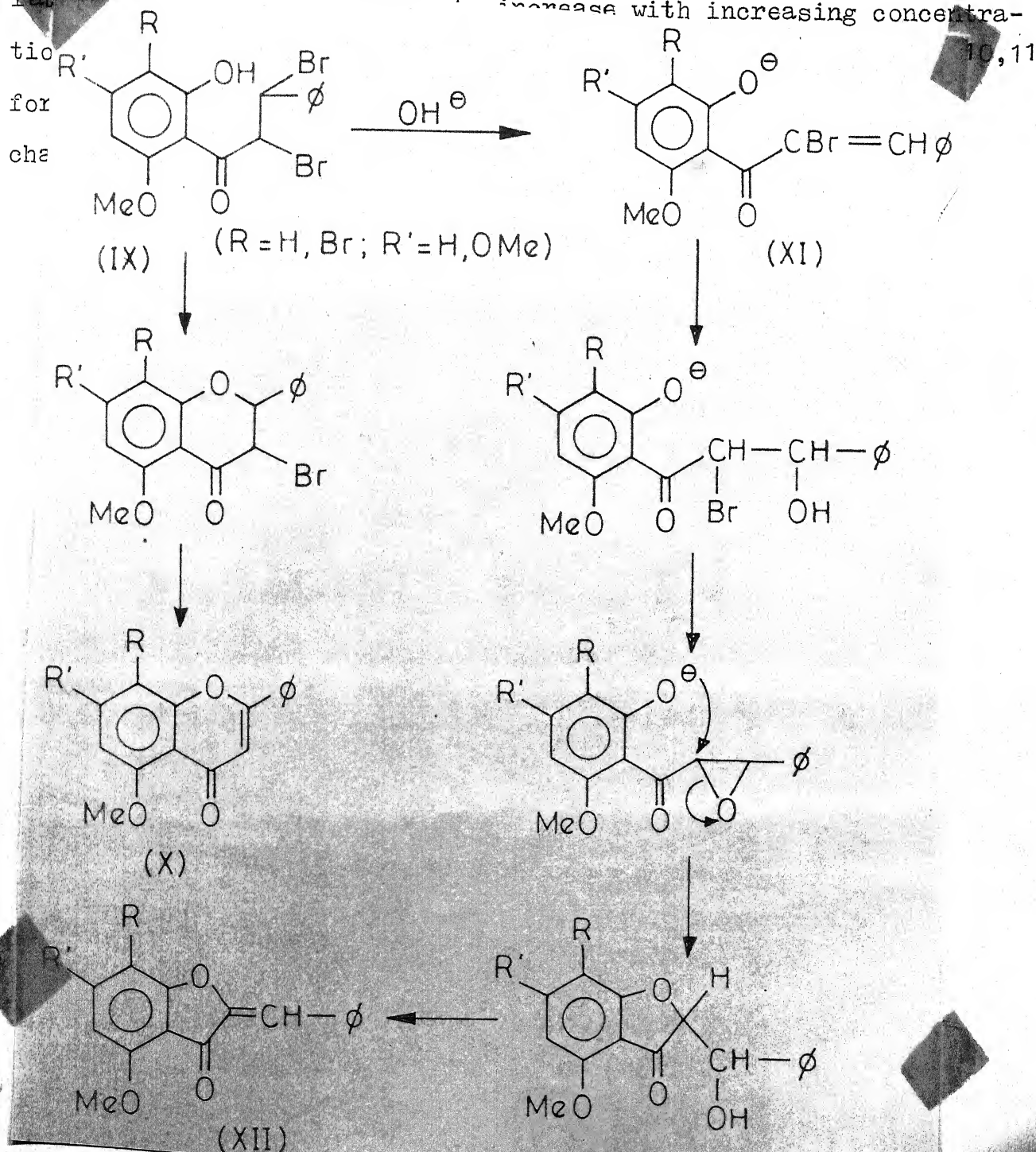
chalcone, which then furnishes the anion (VI). The anion gets protonated and the aurone hydrobromide (VII) loses a molecule of HBr to form the aurone (VIII).

Flavones are generally obtained<sup>7</sup> from 2'-acetoxychalcone dibromides and dichlorides, having a substituent in 6'-position. Aurones, however, are formed when the dihalides carried



substituents both in 3'- and 6'-positions.<sup>7</sup> Apparently steric effect<sup>7</sup> plays an important part in the formation of aurone.

Aurones are produced along with flavones in the reaction of chalcone dibromides with alcoholic potassium cyanide<sup>22</sup> or dilute alcoholic alkali.<sup>2,10,11</sup> The ratio of aurone to flavone in the reaction increases with increasing concentration<sup>10,11</sup>

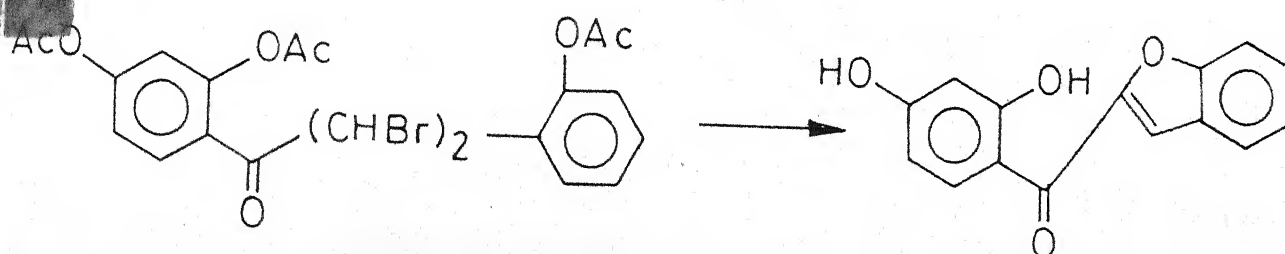




The intermediate  $\alpha$ -bromochalcone (XI) exhibits geometrical isomerism. Its trans isomer cyclises more readily to the corresponding aurone<sup>11</sup> in the presence of base.

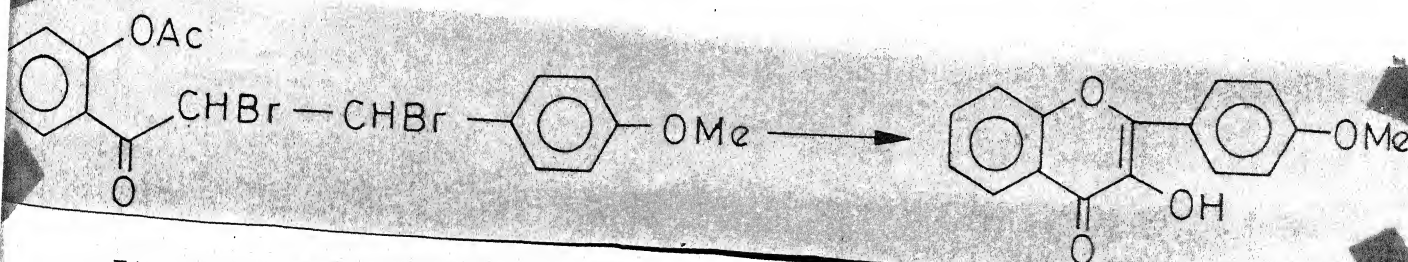
### Benzoylcoumarone:

Some of the o-acetoxychalcones, on treatment with a base yield, the corresponding benzoylcoumarones. The following example is illustrative<sup>12</sup>.



### 2',4'-Dihydroxy-2-benzoyl-Coumarone

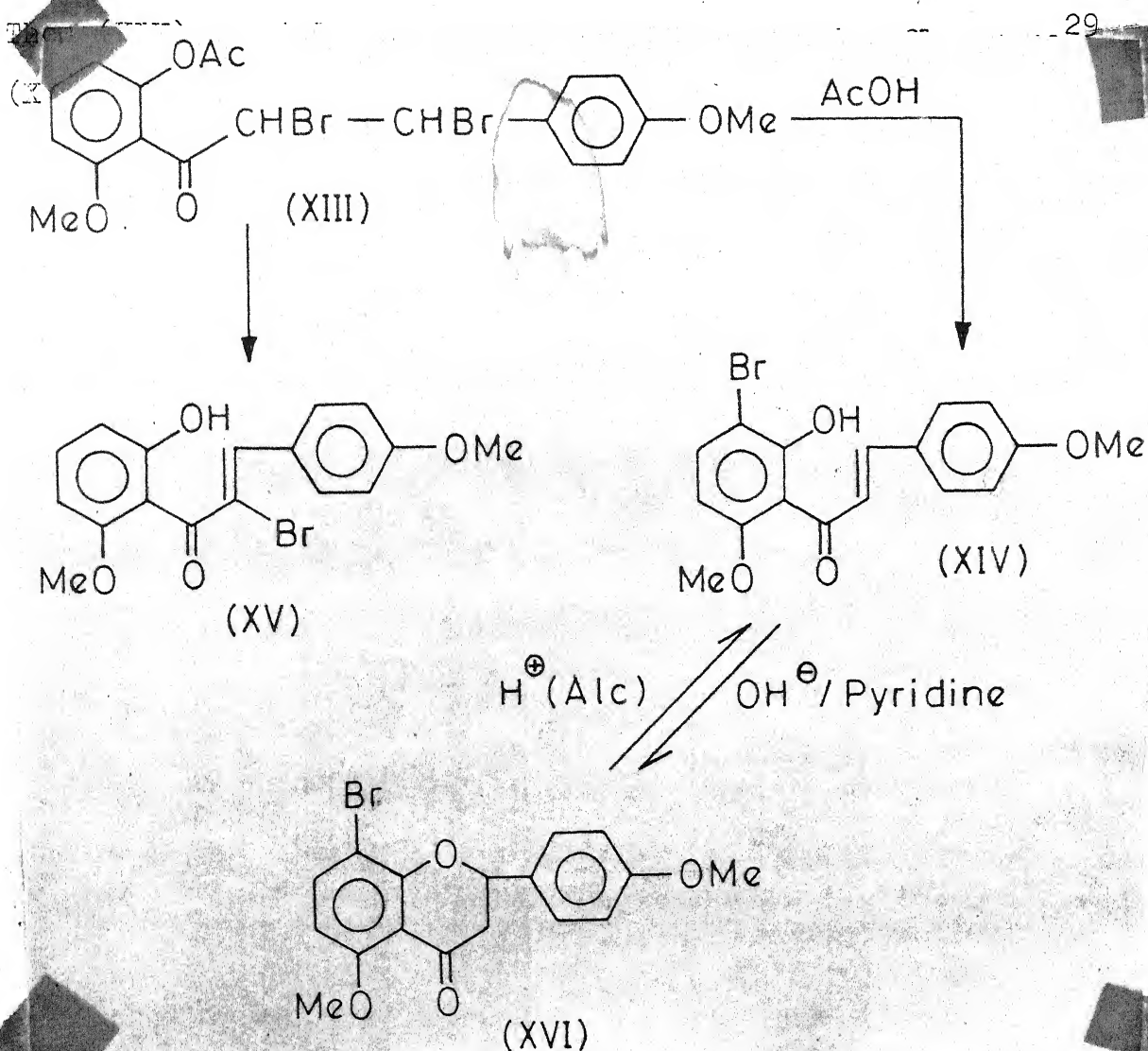
The title compounds have been prepared from appropriately substituted chalcone dibromides. Flavonol,<sup>27</sup> for example, is obtained by the reaction of o-acetoxy chalcone with alkali in aqueous-acetone medium:



It is postulated<sup>28</sup> that the aqueous-acetone replaces the  $\alpha$ -bromine atom with the hydroxyl function and removes two hydrogen atoms.

Flavanones:

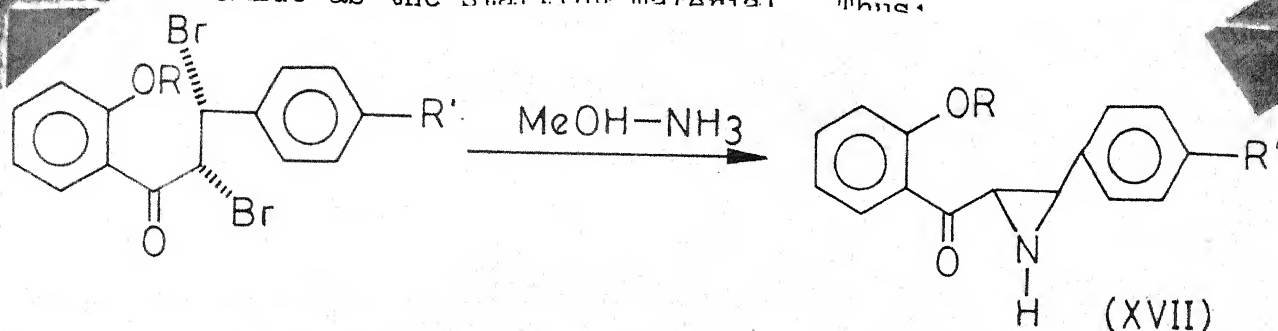
Treatment of 2'-acetoxy-4,6'-dimethoxychalcone dibromide with acetic acid results in deacetylation, debromination, nuclear bromination and the formation of 2'-hydroxy-3'-bromo-4,6-dimethoxychalcone<sup>29</sup> (XIV) and not (XV) as was previously reported.<sup>30</sup>



dibromides can be transformed into a variety of products, viz.,  $\alpha$ -bromochalcones,<sup>22,31</sup> aziridines<sup>5</sup> and aminoflavanones.<sup>5</sup>  $\alpha$ -bromochalcones<sup>31</sup> are obtainable by dehydrobromination of chalcone

dibromides brought about by alcoholic potassium hydroxide.  $\alpha$ -chlorochalcones, however, can be obtained by dehydrochlorination with potassium acetate in absolute ethanol,<sup>32</sup>

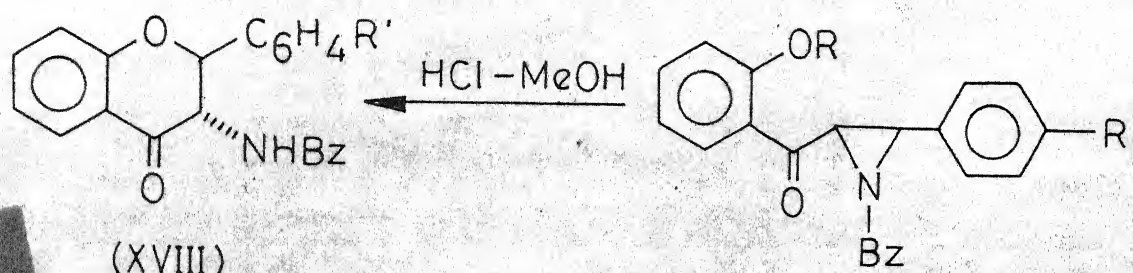
The preparation of aminoflavanones (XVIII), via the aziridine intermediate (XVII) has been accomplished,<sup>5</sup> by using 2'-substituted chalcone dibromide as the starting material. Thus:



$R = \text{CH}_2\phi, \text{CH}_2\text{OMe}$

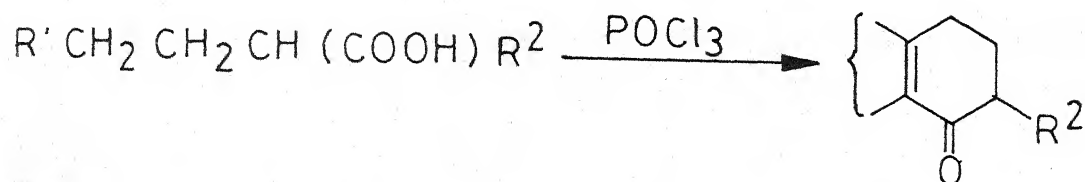
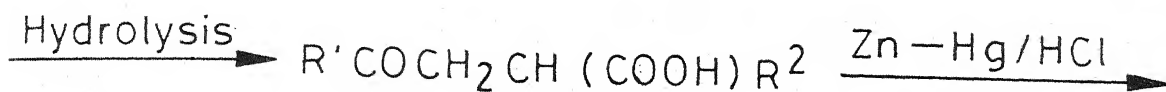
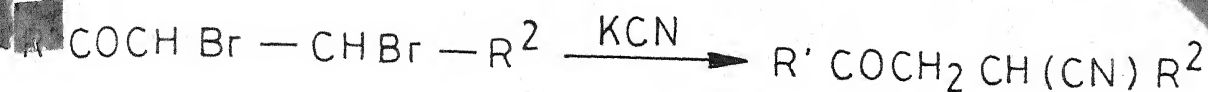
$R' = \text{H}, \text{NO}_2, \text{Cl}$

Benzoylation



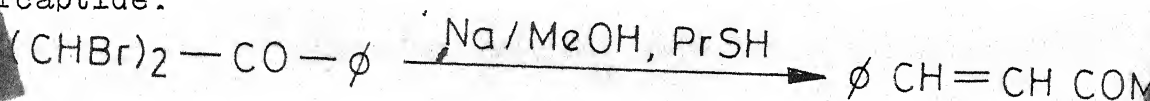
Tetralones:

Chalcone dibromides have been utilized as starting materials for the preparation of 2-aryl-1-tetralone<sup>33</sup> (XIX) by the following sequence of reactions:



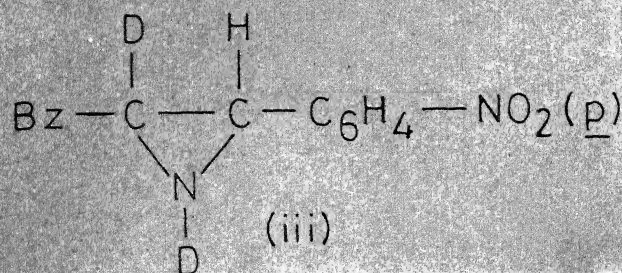
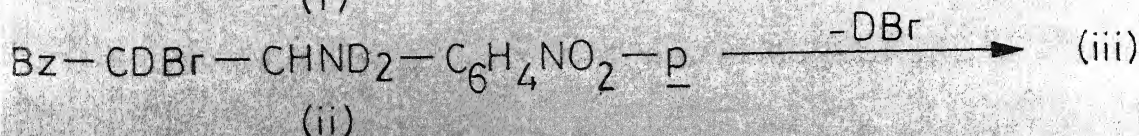
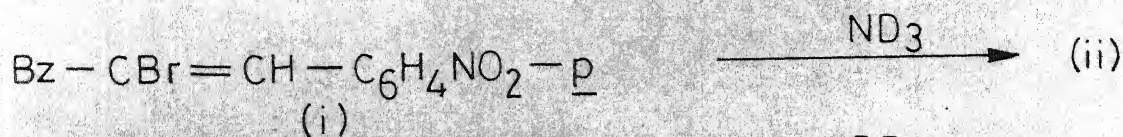
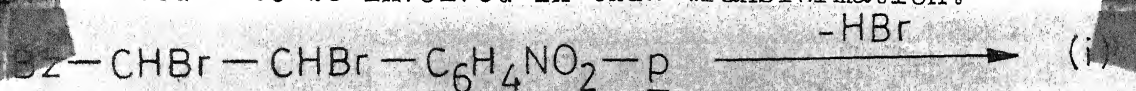
(R' and R<sup>2</sup> are aryl groups) (XIX)

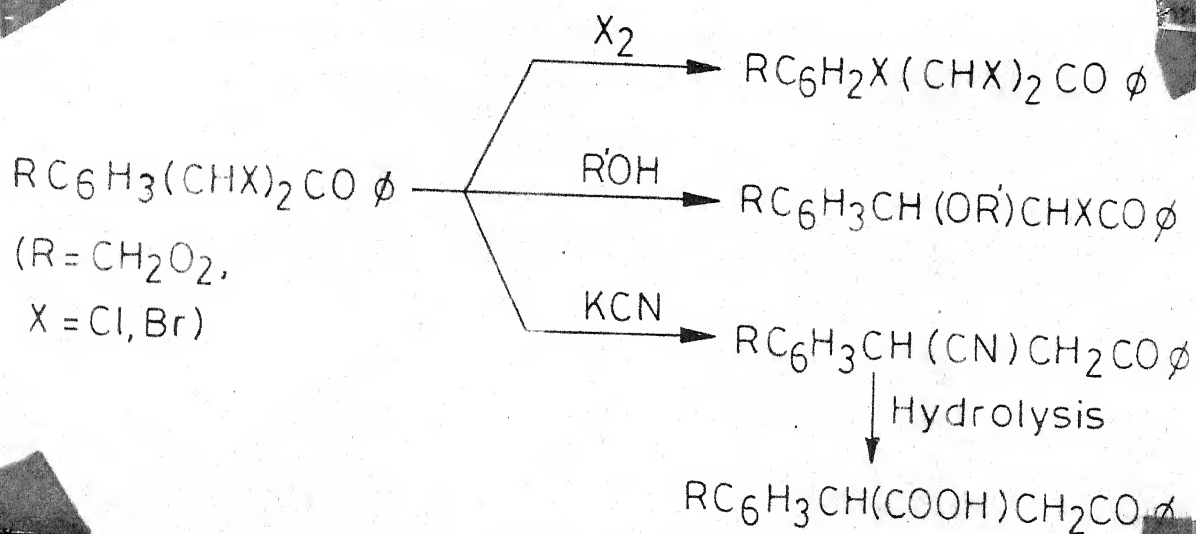
According to a patent, the synthesis of benzalacetone<sup>34</sup> has been effected by the reaction of chalcone dibromide with alkali mercaptide.



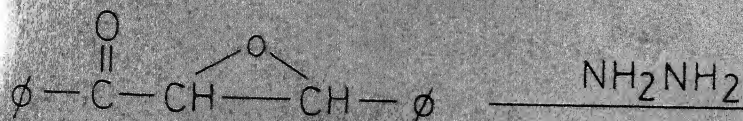
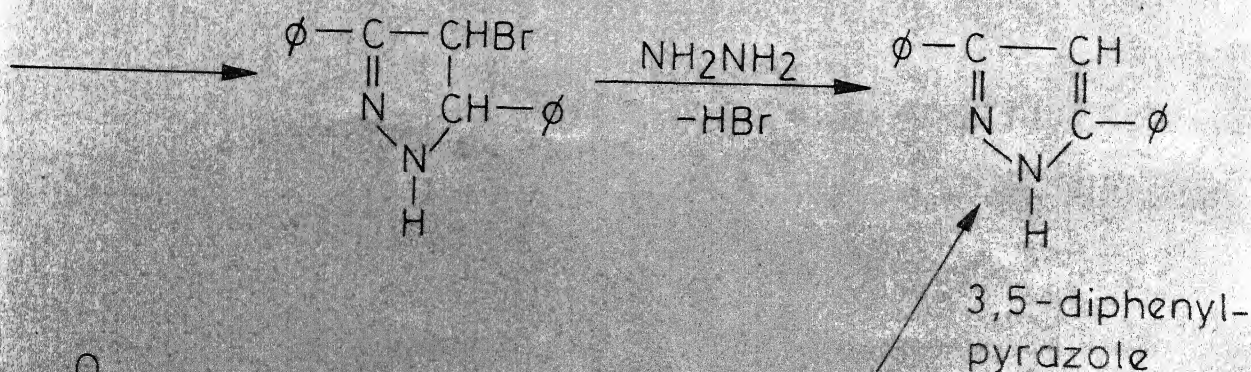
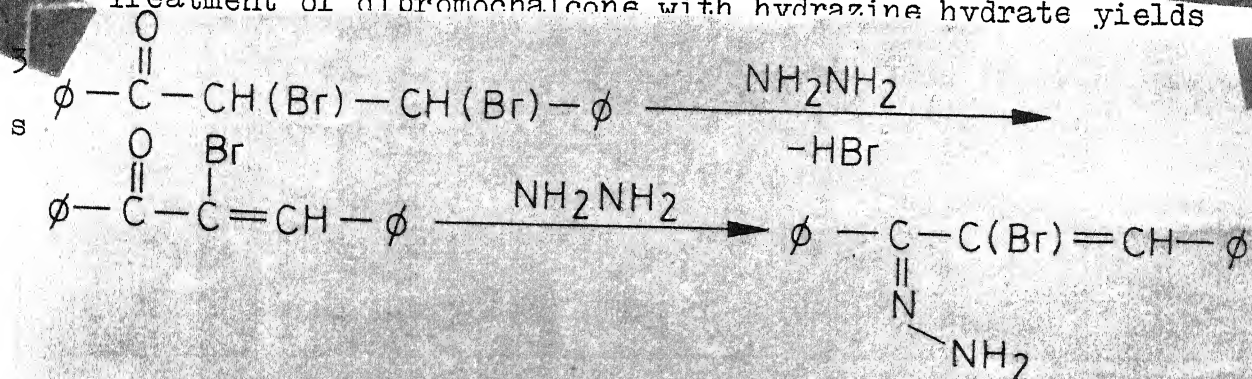
#### Aziridines<sup>35,36</sup>:

Aziridines have been prepared by reacting R'NH<sub>2</sub> (R' = H, Me or Bz) with 4-nitrochalcone dibromide.<sup>36</sup> The following mechanism is postulated<sup>36</sup> to be involved in this transformation:



Miscellaneous Reactions:Reaction with Halogens, Alcohols and Potassium Cyanide:

Treatment of dibromochalcone with hydrazine hydrate yields





### Sodium Azide<sup>39</sup>:

2'-hydroxy (and 2'-benzyloxy) chalcone dibromides are reported<sup>39</sup> to react with sodium azide, leading to the formation of  $\alpha$ -azidochalcones.

### Cleavage of $\alpha$ -bromochalcone with HBr and Oxygen:

$\alpha$ -Bromochalcone (obtained by the dehydrobromination of  $\alpha$ ,  $\beta$ -dibromochalcones) is reported<sup>40</sup> to react with HBr and oxygen in petroleum ether, yielding benzoic acid. 4'-Methyl- $\alpha$ -bromochalcone yields p-toluic acid on similar treatment. These two examples illustrate a novel cleavage reaction, brought about through the oxygen effect.

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CHAPTER - 19

## USES

Sweeteners.....	378
Stabilizers.....	378
Photosensitive Materials.....	380
Polymers.....	381
Scintillators.....	381
Analytical Reagents.....	382
Miscellaneous Applications:	
Polymerization Catalysts.....	382
Fluorescent Whitening Agents.....	382
Organic Brightening Additives.....	382
References.....	382

Many patents have appeared in the literature describing the usefulness of chalcones and their derivatives. Thus these find application as artificial sweeteners,<sup>1-20</sup> stabilizer<sup>21-40</sup> against heat, visible light, ultraviolet light, ageing; colour photography,<sup>55</sup> scintillators,<sup>65</sup> polymerisation catalyst,<sup>68,69</sup> fluorescent whitening agents,<sup>70</sup> organic brightening additives<sup>71,72</sup> etc.

### Sweeteners<sup>1-20</sup>:

Chalcone derivatives, viz., Dihydrochalcones<sup>1</sup> and their corresponding glycosides have been employed as food sweetening agents. Dihydrochalcone xylosides<sup>2</sup> and galactoside,<sup>2,3,10</sup> for example, are claimed to be 1.5-2 times sweeter than saccharin. Incorporation of cyclodextrin with the sweetener-neohesperidin dihydrochalcone,<sup>6,7</sup> is reported<sup>11</sup> to stabilize its aqueous solution. The preparation of a mixture of glucosides<sup>5,8,9</sup> (mono-, di-, tri-, tetra- and penta) of hesperidin dihydrochalcone<sup>4-6</sup> has been described. 3,2',4',6'-Tetrahydroxy-4-propoxy-dihydrochalcone-4  $\beta$ '-neohesperdoside<sup>12</sup> has been used as a synthetic sweetener and is 2,200 times sweeter than glucose.

### Stabilizers:

2',4-Dihydroxy-3,5-di-tert.butylchalcone has been employed as an oxidation inhibitor<sup>21</sup> and stabiliser<sup>22</sup> to polypropylene polymer.

Hydroxychalcones form the starting material for the preparation of hydroxyflavones which serve as antioxidants for lipid material.<sup>23</sup>

Chalcone is a natural constituent of beer and plays, in combination with other polyphenols, an important role in its stability.<sup>24</sup>

Chalcone forms the constituent of corrosion inhibiting lubricants<sup>25</sup> suited for internal combustion engines containing silver and similar metal components. According to one patent<sup>26</sup>

the efficiency of lubricant additive is retained by incorporation of chalcone, otherwise it is diminished by reaction of the additive with olefinic components of base oils or grease.

The incorporation of 2',4,4'-trimethoxychalcone into pulp sheets (on which pesticide was absorbed) helped in retarding the air degradation.<sup>27</sup>

It has been reported<sup>28</sup> that the addition (upto 5%) of chalcone to poly (dimethoxysiloxane)- the silicone dielectric fluid, for impregnation of capacitors etc. improves its dielectric life. Chalcone<sup>29</sup> and  $\beta$ -(benzoyloxy)-2'-hydroxy-chalcone<sup>30</sup> have proved to be good light absorbers and heat stabilizers for polymeric materials, viz., polymethyl methacrylate film and PVC resin sheets. Organic esters having chalcone type skeleton, viz.,  $\text{RC}_6\text{H}_3(\text{OH})\text{COCH}=\text{C}(\text{OOC}_6\text{H}_5)_2$  [where R=Br or H] have been employed for the aforesaid purpose.<sup>31</sup>

Incorporation of 0.02-5% chalcone is claimed to prevent discoloration of microcrystalline petroleum waxes<sup>32</sup> and polymers<sup>33</sup> (halogen containing polyvinyl compounds) exposed to sunlight. Likewise polyolefins are stabilized<sup>34</sup> against light, heat as well as ageing by adding small amount of chalcone.

Chalcone has been described to possess uv absorption property and hence finds application as uv absorption filters.<sup>35,36</sup>

Chalcone serves as a suitable ultraviolet absorption additive<sup>37</sup> in adhesives, lacquers and plastics.

A non-irritating preparation containing 1-5% chalcone, for the protection<sup>38,39</sup> of skin from sunlight, has been patented.

It is reported<sup>40</sup> that the properties of cellulosic material are improved with ionization radiations in the presence of graftable organic finishing agent, consisting of chalcone and a sensitizer.

#### Photosensitive Materials:

A number of chalcone derivatives<sup>22,41-47</sup> form the principle ingredients in the preparation of photosensitive polymeric material, some of which possess good film forming properties.<sup>42</sup>

Photocross linkable copolymers<sup>48</sup> are used for the preparation of sharp relief images and printing blocks, printing of multilayer circuits.<sup>49</sup> The printed image in the latter case is claimed to be of high edge sharpness.

Light sensitive preparations useful for printing plates of improved sensitivity and resolution are described<sup>50-53</sup> which, for example, involve the reaction of 4'-(2-hydroxyethoxy) chalcone with styrene-maleic anhydride copolymer under appropriate conditions.

Another light sensitive resin has been reported<sup>54</sup> which possesses good characteristics in respect of adhesion, toughness, alkali resistance and stability towards oxidation. The resin has been obtained<sup>54</sup> by heating 3,4'-dihydroxychalcone with an epoxyresin in a suitable solvent, in the presence of alkali.

Chalcone, 4-isocyanato(chalcone and furan analogue of chalcone have proved useful in the preparation of light sensitive film used in colour photography.<sup>55</sup> Chalcone is also used in the preparation of photo-thermographic emulsion.<sup>56</sup>

4,4-Diphenylaminochalcone<sup>57</sup> and 4,4'-bis (diphenylamino) chalcone<sup>58,59</sup> have been used as constituents of a photoconducting composition for use in electro-photographic products.

Photographic silver halide emulsion spectrally sensitized with carbocyanine dyes, can be supersensitized<sup>60</sup> with some chalcones, viz., 2' (and 4')-chlorochalcones.

#### Polymers:

Dihydroxychalcone has been used<sup>61,62</sup> for the preparation of uncured epoxyresins. 4,4'-Dihydroxychalcone forms the component of a duroplastic mixture,<sup>63</sup> which possess good mechanical properties and a high thermal stability.

Methacryloyloxychalcones are used as cross linking agents<sup>64</sup> in the preparation of butyl acrylate-styrene copolymers, which are claimed<sup>64</sup> to be useful as lacquers.

#### Scintillators:

2,4,6-Trisubstituted pyridines, derived from chalcones and formamide (Leuckart reaction), exhibit extremely intense fluorescence and could be used as scintillators.<sup>65</sup>

### Analytical Reagents:

Chalcones react with a number of metal ions and are reported<sup>66</sup> to be more reactive than the aldehyde or ketone from which they have been prepared. This reaction has been exploited<sup>67</sup> for the detection of  $\text{Fe}^{+++}$  (limit of identification: 0.33  $\gamma$ /0.05 ml) by 2',4'-dihydroxychalcone, provided the concentration of interfering ions is kept at a minimum.

### Miscellaneous Applications:

#### Polymerisation Catalysts, Fluorescent Whitening Agents and Organic Brightening Additives:

Chalcone is reported<sup>68,69</sup> to form a component of a polymerisation catalyst designed for obtaining a highly crystalline polyolefinic polymers, viz., polyacrylates, in high yields.

Chalcone sulphonic acids serve as intermediates in the preparation of fluorescent whitening agents.<sup>70</sup> Chalcones have also been employed as organic brightening additives.<sup>71,72</sup>

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Author Index

The numbers in parentheses are the reference numbers.

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|----------------------|------------------|
| Abbe, N.J.V.         | Akhmookh, Y.     |
| Abbott, U.K.         | Akhmedzade, D.A. |
| Abdalla, M.          | Alexa, V.        |
| Abdel-Halim, M.S.    | Algar, J.        |
| Abdel-Maksoud, A.    | Allen, C.F.H.    |
| Abdel-Megeid, E.M.F. | Allen, J.M.      |
| Abdel-Moez, M.S.     | Ambekar, S.Y.    |
| Abdel-Rahman, S      | Amin, G.C.       |
| Abe, S.              | Anand, N.        |
| Abell, R.D.          | Anderson, J.R.   |
| Abramovich, B.       | Ando, J.         |
| Abrazhevich, A.I.    | Andrew, L.J.     |
| Acharya, S.          | Andrews, D.B.    |
| Adachi, Y.           | Andrieu, C.      |
| Adams, J.H.          | Angdi, S.D.      |
| Adityachaudhury, N.  | Anonimova, I.V.  |
| Agarwal, S.C.        | Ansari, M.A.     |
| Ahluwalia, V.K.      | Anteunis, M.     |
| Ahmad, S.            | Anthonsen, T.    |
| Ahuja, A.P.          | Antus, S.        |
| Akabori, Y.          | Aoki, K.         |
| Akaboshi, S.         | Arbuzov, B.A.    |

Arens, J.F.

Aries, R.

Aritomi, M.

Ariyan, Z.S.

Arnason, B.

Arnould, J.C.

Arora, R.

Arora, S.K.

Artemenko, A.I.

Arventiev, B.

Asahina, I.

Asaumi, S.

Ash, M.L.

Atchabba, F.A.

Atkinson, R.B.

Aubry, C.

Aurnhammer, G.

Auwers, K.V.

Avakian, S.

Avramovici, S.

Awad, W.I.

Ayabe, T.

Baba, K.

Babu, S.S.

Baciu, A.

Bader, H.J.

Badiger, V.

Badoche, M.

Baeyens, P.

Baez, R.

Bajusz, S.

Bajwa, B.S.

Bala, S.

Balaban, A.T.

Balaiah, V.

Ballio, A.

Balogh, L.

Bandlows, C.

Banerji, A.

Ban'kovski, A.I.

Bannerjee, N.R.

Bar, D.

Baranac, J.M.

Baranov, S.N.

Barber, E.D.

Bargellini, G.

Barker, S.A.

Barnes, R.P.

Barrio, G.

Barrio, J.R.

Bartsch, W.

Barua, A.K.

Barua, R.N.

Barz, W.

Basso, A.J.

Bastide, J.D.

Bates, R.B.

Baudrenghien, J.

Bauer, E.

Bauer, R.C.

Baumgartel, H.

Bayer, F.

Beaucaire, V.D.

Becker, H.

Beerens, H.

Behera, G.B.

Behnisch, R.

Beiler, J.M.

Beilstein, F.

Bellamy, L.J.

Bellino, A.

Belotsvetov, A.V.

Belous, G.G.

Belyaev, V.F.

Bendal, D.S.

Ben-Dor, L.

Bennett, E.B.

Bennett, P.

Beno, A.

Berdahl, J.M.

Berestetskaya, V.D.

Berezina, S.I.

Berge, D.D.

Bergl, F.

Bergmann, E.

Berlin, J.

Bertrand, J.

Bestmann, H.J.

Betin, O.I.

Betts, B.E.

Beumel, O.F. (Jr.)

Beynon, J.H.

Bezuglyi, V.D.

Bhagwat, N.A.

Bhakuni, D.S.

Bhardwaj, D.K.

Bhaskar, A.



- Bhat, A.R.  
Bhatia, V.K.  
Bhatt, S.  
Bickel, C.L.  
Bigland, C.H.  
Bilech, H.A.  
Bini, L.  
Biradar, N.S.  
Birkeland, S.P.  
Birkofer, L.  
Bittner, M.  
Blac-Guenee, J.  
Black, W.B.  
Blain, Y.  
Blankenburg, C.  
Blatt, A.H.  
Blecker, H.H.  
Bloodworth, A.J.  
Blume, J.  
Boberov, O.F.  
Bodani, D.C.  
Bodani, V.V.  
Boerwinkle, F.  
Bogert, M.T.  
Bognár, R.  
Bohm, B.A.  
Boichard, J.  
Bokadia, M.M.  
Boland, M.J.  
Boleski, H.  
Bolla, F.  
Bond, J.C.  
Bondarenko, V.E.  
Bonte, J.P.  
Bonvicini, A.  
Borisov, M.I.  
Borodin, V.N.  
Boross, F.  
Borovoi, I.A.  
Bos, H.J.T.  
Rose, A.K.  
Bose, K.  
Bose, P.K.  
Botelho, H.C.  
Bottini, A.H.  
Bowie, J.H.  
Boykin, D.W. (Jr.)  
Bozak, R.E.  
Bradley, J.S.  
Bradt, E.V.

Bradt, W.	Budagyants, M.I.
Bradway, C.J.	Bugai, A.I.
Brady, B.A.	Burlaka, V.P.
Bramley, R.	Burton, G.W.
Branch, G.	Buryakovskaya, E.G.
Branch, G.E.K.	Butkiewicz, K.
Braude, E.A.	Buu-Hoi, N.P.
Braun, W.	Buza, D.
Bravo, P.	Buzas, A.
Bremer, K.	
Breslow, D.S.	
Brian, P.W.	Cabak, J.
Brockmann, H.	Caccamese, S.
Brodie, A.M.	Cahn, J.
Brosche, K.	Calcinari, R.
Brosche, K.C.	Calloway, N.O.
Brown, B.R.	Campbell, D.
Brown, W.G.	Campbell, N.
Browne, C.L.	Cardillo, B.
Bruce, D.B.	Cardillo, G.
Bruce, R.J.	Carpena, O.
Bruderlein, F.	Carretto, J.
Bub, O.	Carrie, R.
Budel, O.N.	Carsky, P.
Buckman, S.J.	Cascaval, B.

Cashman, M.	Chauvelier, J.
Cason, L.F.	Chawla, H.M.
Caughlan, J.A.	Chaykovsky, M.
Cavina, G.	Chekmaeva, G.E.
Cazin, M.	Chem, F-C.
Cernak, J.	Chen, C.I.
Cezza, A.	Chen, C-Y.
Chabannes, B.	Chen, F-C.
Chadha, K.L.	Chen, P.
Chadha, M.S.	Chen, T-K.
Chadwell, H.M.	Chen, Y-L.
Chadwick, T.C.	Chernobai, V.T.
Chaganty, R.B.	Chervova, A.V.
Chakrabarti, S.	Chervenyuk, G.I.
Chakravarti, D.	Chhatriwala, K.M.
Chakravarti, P.	Chhaya, G.S.
Chambers, R.D.	Chiang, S-H.
Chanda, B.K.	Chiba, T.
Chang, C-T.	Chibber, S.S.
Ch'ang, K-S.	Child, R.G.
Chang, P.W.	Chizhov, O.S.
Chapin, E.C.	Chopin, J.
Chardonnens, L.	Choughuley, A.S.U.
Chatterjee, A.	Chowdhury, A.
Chatterjee, J.N.	Christensen, E.

Christman, D.R.	Conant, J.B.
Churkin, Y.D.	Conley, R.A.
Cichy, B.	Conn, J.E.
Clagett, D.D.	Connor, R.
Clark, J.P.	Contois, L.E.
Clark, S.F.	Coombs, E.
Clark, T.J.	Corey, E.J.
Clark-Lewis, J.W.	Cormier, R.A.
Claude, A.	Cornilleau, J.
Clayton, T.	Cornubert, R.
Clinton, R.O.	Corvaisier, A.
Cobern, D.	Covello, M.
Coelho, J.S. de B.	Cricchio, R.
Cohen, A.	Criegee, R.
Cohen, H.	Cristol, S.J.
Cohen, M.	Crombie, L.
Cohen, R.	Cromwell, N.H.
Cole, J.R.	Cross, B.
Cole, J.W.	Cseh, I.
Cole, W.	Csendes, E.
Coleman, L.E.	Csuros, Z.
Colonna, S.	Cullen, W.P.
Columba, C.	Cummins, B.
Combes, G.	Curtze, A.
Compagnini, A.	Cutter, H.B.

Czelenyi, C.	Decoret, C.
Czira, G.	Dedieu, M.
Czukur, B.	Deeb, A.
	De Eds. F.
	Deev, A.I.
D'amore, G.	Delassue, H.
Dandeganoker, S.H.	Delavigne, R.
Danderova, M.	Delcarmen, M.
D'Arcangelo, A.T.	Delius, M.M.
Das, S.C.	Delle Monache, F.
Dashevskii, M.M.	Delle Monache, G.
Datta, S.C.	Dement, W.A.
Daubner, H.	De Oliveria, A.B.
Davey, W.	Desai, H.K.
David, E.	Deshmukh, B.K.
David, E.R.	Deshmukh, G.V.
Davidson, A.J.	Deshpande, S.S.
Davies, R.G.	De Simone, F.
Davis, H.L.	Deutsch, D.H.
Deak, G.	Deutsch, S.
Dean, F.M.	Devitt, P.F.
Debard, R.	De Vlaming, P.
De Benneville, P.L.	Dewar, D.
De Blic, A.	Dewar, D.J.
Debruyne, Mme. E.	Dewick, P.M.

Dhar, D.N.	Doran, H.J.
Dhar, M.M.	Dore, J.C.
Diakur, L.N.	Dorofeenko, G.N.
Diehr, H.J.	Dornow, A.
Diekmann, J.	Doucet, J.P.
Dilthey, W.	Drefahl, G.
Dini, A.	Drewes, S.E.
Dinkar	Drobnica, L.
Dinklage, R.	Dubnitskaya, V.I.
Dinya, Z.	Duclos, J.P.
Dippy, J.F.J.	Dudas, T.
Divakar, N.G.	Duerr, H.
Dobo, I.	Dufraisse, C.
Dobretsov, G.E.	Duke, P.J.
Dodson, R.M.	Duperray, B.
Dodwadmath, R.P.	Dupre, R.A.
Doering, H.W.	Durand, J.
Doering, W.V.E.	Durinda, J.
Dolter, R.J.	Dutta, C.P.
Dombrovskii, A.V.	Dutta, J.
Do-Nascimento, M.C.	Dutta, S.P.
Donnelly, D.J.	Dzurilla, M.
Donnelly, D.M.X.	Dzyuba, V.P.
Donnelly, J.A.	
Donskova, A.I.	

- Eades, J.F.  
Eaton, J.K.  
Ebert, E.  
Efimov, A.A.  
Egger, H.  
Eggert, H.G.  
Ehrig, B.  
Eichwald, E.  
Eiduson, S.  
Eisenbraun, E.J.  
Eisenlohr, F.  
Eistert, B.  
El-Agamey, A.A.  
El-Baya, A.W.  
El-Bayouki, K.  
Elkasaby, M.  
Elkaschef, A.F.  
Elkerdawy, M.M.  
Ellert, H.G.  
Elnagdi, M.H.  
El-Neweihy, M.F.  
El-Sayed, A.S.  
El-Zimaity, M.T.  
Emmons, W.D.  
Endo, T.  
Endress, R.  
Enebäck, C.  
Engels, H.D.  
Essawy, A.  
Evans, D.P.  
Evard, F.  
Eveleigh, D.E.  
Exner, J.  
Ezaki, S.  
Fabre, P.S.A.  
Fahmy, A.F.  
Falcao da Fonseca, L.  
Farkas, I.  
Farkas, L.  
Farkas, M.  
Favorskaya, I.A.  
Favre-Bonvin, J.  
Fazliev, D.F.  
Fedorov, L.A.  
Fedyunina, G.M.  
Feigl, F.  
Ferguson, L.N.  
Fernandes de Albuquerque, M.M.

Ferrara, L.	Francisco de Mello, J.
Terreira, D.	Fraser, A.W.
Field, L.	Frederick, J.
Fields, E.K.	Frenzel, H.
Filler, R.	Freon, P.
Finch, L.R.	Frese, A.
Finkel'shtein, A.V.	Frezouls, J.
Finkelstein, M.	Friedrich, L.E.
Finnegan, R.A.	Fries, J.
Fischer, F.	Friess, S.L.
Fisera, L.	Fromm, E.
Fishman, N.	Fujise, S.
Flammang, M.	Fujishige, M.
Flanagan, K.J.	Fuka, A.
Flemming, C.L. (Jr.)	Fukomoto, J.
Fletcher, H.	Fukuda, J.H.
Flynn, J.P.	Fukushina, D.K.
Folsom, T.L.	Fukuto, T.R.
Fontijn, F.	Fullhart, L.
Ford, M.E.	Fundyler, I.N.
Forgione, P.	Funke, A.
Forkmann, G.	Furuya, T.
Formanek, K.	Fuson, R.C.
Fourie, T.G.	
Fox, C.J.	



Gabe, I.	Gilbert, R.I.
Gabor, M.	Gillespie, R.J.
Galust'yan, G.G.	Gillet, A.
Garcia, E.N.	Gilman, H.
Gasha, M.	Giovambattista, N.
Gautier, J.A.	Giri, S.
Geczy, I.	Glennie, C.W.
Geiger, W.B.	Glover, C.A.
Geissman, T.A.	Gocheva, V.
Geller, E.	Goggin, P.
Gennaro, A.	Golovanova, Y.I.
Gentili, B.	Goncharenko, G.A.
George, M.	Gonclaves de Lima, O.
George, M.V.	Gono, E.
Georgi, R.	Gore, K.G.
Ghate, C.G.	Gore, P.H.
Gheorghiu, C.V.	Gormley, T.R.
Ghiya, B.J.	Gorrichon, L.
Gholse, S.B.	Gorrichon-Guigon, L.
Ghuja, B.J.	Gottlieb, O.R.
Giannasi, D.G.	Gottsegen, A.
Gibian, H.	Gouret, C.
Gierse, D.	Govindachari, T.R.
Giese, A.C.	Grabarkiewicz, J.
Giese, H.	Grabovskaya, V.V.

Gradgeorge, M.	Guilt, J.R.
Graff, M.	Guinchard, C.
Graham, J.H.	Gulevich, V.V.
Grambow, H.J.	Gunder, O.A.
Grammaticakis, P.	Gundersen, A.
Gramstad, T.	Gunther, M.
Green, B.S.	Gupta, L.
Green, C.	Gupta, R.C.
Green, L.D.	Gupta, R.K.
Grigg, R.	Gupta, S.K.
Grin, L.M.	Gupta, S.R.
Grinew, G.V.	Gupta, V.P.
Gripenberg, J.	Guthrie, J.L.
Grisebach, H.	Guy, J.
Grishko, L.G.	Gwilt, J.R.
Groen, M.B.	Gyoryova, K.
Grouiller, A.	
Gruber, R.	
Grunfest, M.G.	Haensel, R.
Grushevich, V.I.	Haginiwa, J.
Gryff-Keller, A.	Hahlbrock, K.
Gubenko, N.T.	Hahn, L.V.
Gubler, H.	Haines, R.M.
Gudi, N.	Haisa, M.
Guettler-Pimenidou, E.	Halban, H.V.

Hamada, M.	Hatanaka, H.
Hamed, A.A.	Hatayama, K.
Hamilton, L.A.	Hattori, S.
Hammond, G.	Hattori, T.
Hamrick, P.J. (Jr.)	Hauser, C.R.
Hankovsky, O.H.	Hawker, C.D.
Hannah, J.	Haworth, J.W.
Hänsel, R.	Hayakawa, G.
Hanson, G.A.	Hayasaka, K.
Harhash, A.H.	Hayashi, M.
Harrand, M.	Hayashi, N.
Harris, G.C.	Hayashi, S.
Harris, T.M.	Hayashi, Y.
Hart, B.F.	Hayes, W.P.
Hartmann, H.	Hearnes, J.A.
Hase, J.	Hecaen, Y.
Hase, T.	Heger, J.
Hasebe, N.	Heilbron, I.M.
Hasegawa, M.	Heinz, J.
Hashiba, A.	Heller, L.
Hashigaki, K.	Helmkamp, R.W.
Haske, B.J.	Hemming, H.G.
Hassner, A.	Henning, H.
Hata, K.	Henrich, F.
Hataba, A.M.	Henry, D.W.

Hensel, A.	Hořak, V.
Henze, H.R.	Horakova, K.
Hergert, H.L.	Hörhammer, L.
Hertz, W.	Horiguchi, T.
Hertzler, D.V.	Horowitz, R.M.
Hidayetulla, M.A.	Horton-Dorge, M.
Hideg, K.	Hosokawa, S.
Hiemstra, H.	Hosni, G.
Higashi, N.	House, H.O.
Higuchi, Y.	Hrabovsky, J.
Hikichi, M.	Hsu, C-L.
Hilda, W.	Hsu, K.K.
Hill, D.G.	Hubert, E.
Hinkley, D.F.	Huet, J.
Hirano, H.	Hugel, R.
Hiremath, S.	Hughes, E.G.
Hirose, K.	Huls, R.
Hochstein, F.A.	Humphlett, W.J.
Hoffmann, H.	Hutchinson, W.A.
Holak, F.A.	Huthwelker, W.
Holden, N.E.	
Holland, W.	
Holler, H.	Ibrahim, M.A.
Holzenger, A.	Ibrahim, S.
Horak, M.	Ichibashi, T.

Ichii, K.	Ivanova, E.T.
Ichijo, T.	Iwakura, Y.
Igasa, H.	Iyer, R.N.
Iimura, F.	Izumi, T.
Iinuma, M.	Izvekov, V.P.
Ikeda, H.	
Ikeda, K.	
Imoto, M.	Jackson, B.
Imperato, F.	Jackson, E.L.
Inque, T.	Jackson, W.R.
Inskip, H.K.	Jacob, D.
Iovchev, A.	Jacob, K.C.
Iqbal, M.	Jadhav, G.V.
Iseki, K.	
Ishida, R.	Jadot, J.
Ishida, S.	Jahine, H.
Ishii, K.	Jain, A.C.
Itagaki, Y.	Jain, S.C.
Ito, M.	Janisch, H.
Ito, N.	Janistyn, B.
Ito, T.	Janssens, W.
Ivanov, G.	Janzso, G.
Ivanov, D.	Jarboe, C.H. (Jr.)
Ivanov, K.	Jarman, D.A.
Ivanov, N.V.	Jauhar, A.K.

Jay, M.	Joshi, U.G.
Jekel, P.	Joshi, V.
Jemison, R.W.	Josty, P.L.
Jeney, E.	Jullian, P.L.
Jensen, S.R.	Jungk, A.E.
Jeppson, J.	Jurasek, A.
Jerchel, D.	Jurd, L.
Jerzmanowska, Z.	
Jha, B.C.	
Jhaveri, L.C.	Kabiev, O.K.
Johnson, B.F.G.	Kachurin, O.I.
Johnson, D.K.	Kagan, J.
Johnson, G.D.	Kakkar, S.N.
Johnson, R.S.	Kalckbrenner, E.
Johnson, W.S.	Kallay, F.
Johnston, K.M.	Kalle, A-G.
Jolad, S.D.	Kalmar, A.
Jone, M.	Kametani, T.
Jones, F.B.	Kamiya, S.
Jones, J.F.	Kamoda, M.
Jones, R.G.	Kanate, B.
Jordan, R.H.	Kang, H.H.
Jorgenson, M.J.	Kang, J.W.
Joshi, K.C.	Kanomate, K.
Joshi, R.S.	Kanthi, R.B.

Kao, Chen-Heng	Kawai, W.
Kao, Chung-Hsi	Kawalek, B.
Kaplash, B.N.	Kawamura, Y.
Kar, J.N.	Kawasaki, T.
Kardos-Balogh, Z.	Kawashima, T.
Karel, V.	Kayano, M.
Kargin, Y.M.	Kazak, R.V.
Kargina, N.M.	Keegan, J.R.
Karlsruhe, R.E.	Keenan, A.K.
Kasahare, A.	Keenan, P.J.
Kashino, S.	Kelkar, A.S.
Kasiwagi, V.H.	Kellog, R.M.
Kasprzyk, H.	Kenji, T.
Katagiri, T.	Khadikar, P.V.
Katayama, A.	Khadzhai, Y.I.
Katiyar, S.S.	Khandual, N.C.
Kato, M.	Khanna, R.N.
Katsui, G.	Khanolkar, A.P.
Katzenellenbogen, E.R.	Kharasch, M.S.
Kauffmann, H.	Kharat, R.B.
Kaufmann, H.P.	Kharchenko, V.G.
Kaul, D.K.	Khashchina, M.V.
Kaushal, K.	Khazanchi, R.
Kavka, J.	Khilya, V.P.
Kawagoe, M.	Kho, K.F.F.

Khudabaksh, A.R.

Kickuth, R.

Kieser, F.

Kihara, Y.

Kim, S.M.

Kinastowski, S.

Kindler, K.

King, B.

King, H.G.C.

King, P.A.

Kinugasa, H.

Kirby, R.H.

Kirlyanova, R.P.

Kirtaniya, C.L.

Kishimoto, Y.

Kiss, A.I.

Kiss, P.

Kitaev, Y.P.

Kleu, H.

Klinke, P.

Klykova, L.V.

Knoppova, V.

Ko, K.

Kobashi, K.

Kobayashi, R.

Kochetkov, N.K.

Koelbel, H.

Koelsch, C.F.

Kohler, E.P.

Kohlrausch, K.W.F.

Kohman, T.P.

Kojkiewicz-Balcerek, M.

Kolena, J.

Kolesnikov, I.G.

Kollar, V.

Kolodyazhnyi, Y.V.

Komatsu, M.

Komatsu, T.

Konate, B.

Konishi, T.

Koningsberger, C.

Konno, K.

Kononovich, V.I.

Korn, F.

Korotkov, S.A.

Korponai, K.

Korshunova, I.A.

Korshunova, K.M.

Kostanecki, S.V.

Korton, M.M.



Koudsi, Y.	Kulkarni, V.G.
Kovac, J.	Kulkarni, V.H.
Koval, L.N.	Kunii, T.
Kovalev, I.P.	Kunze, W.
Kowac, W.	Kurihara, Y.
Koyama, T.	Kuroda, C.
Kozawa, M.	Kuroiwa, M.
Kozlov, N.S.	Kurokawa, T.
Krasnaya, Z.A.	Kurosawa, K.
Krasoviskii, B.M.	Kurosawa, T.
Kratzer, O.	Kursanov, D.N.
Kratzl, K.	Kurth, E.F.
Krijl, G.	Kurumi, M.
Krishena, B.M.	Kushwaha, S.C.
Krishnamurti, M.	Kuskov, V.K.
Krishnamurty, H.G.	Kutsenko, L.M.
Kristian, P.	Kutsuma, T.
Krueger, R.	Kutulya, L.A.
Kubat, K.	Kuyama, H.
Kucherenko, A.P.	Kuzmina, Z.M.
Kucherov, V.F.	Kyogoku, K.
Kuhn, B.	
Kuhn, L.P.	
Kuivila, H.G.	
Kulkarni, A.B.	

Labbe, B.G.

Labiaun, O.

Lachmann, C.

Lafon, L.

Lal, J.B.

Laliberate, R.

Lalithamibika, M.

Lam Ngok Thiem

Lange, G.

Langhammer, L.

Langlais, M.

Lapworth, A.

Latif, N.

Laukhina, L.T.

Laur, J.

Lavin, T.P.

Laviron, E.

Lavrushin, V.F.

Lawesson, S.O.

Lázár, J.

Lebedev, O.P.

Lecomte, J.

Lee, G.A.

Lee, S-T.

Le Fevre, R.J.W.

Leisten, J.A.

Lelyukh, L.I.

Leonard, N.J.

Leoncio d' Albuquerque, I.

Lenka, S.

Lense, F.T.

Lesieur, D.

Lesieur-Demarquilly, I.

Leska, J.

Lespagnol, A.

Lespagnol, C.

Lester, G.R.

Leusink, A.J.

Levai, A.

Levin, K.

Lewis, J.

Lewis, J.R.

Lewis, J.W.

Lewis, R.L.

Liberti, A.

Limaye, S.D.

Lin, C-H.	Lupi; A.
Lin, Y-C.	Luttringhaus, A.
Lin, Y-Y.	Lutz, R.E.
Lindenbaum, S.L.	Luwisch, M.
Lindner, K.	Lyra, F.D. de A.
Linke, H.A.B.	
Linstead, R.	
Litkei, G.	Mabry, T.J.
Litvin, I.Y.	Mack, P.O.L.
Litvinenko, E.V.	MacLean, I.S.
Litvinenko, V.I.	Magdeeva, R.K.
Lo, M.S.	Magnani, A.
Lockett, M.F.	Mahal, H.S.
Locksley, H.D.	Mahanta, B.C.
Lodh, S.B.	Mahanth, P.
Loerch, R.K.	Main, L.
Lora-Tomayo, M.	Maksyutina, N.P.
Lorentzen, G.B.	Malashko, P.M.
Losert, E.	Malbee, F.
Loth, H.	Malik, S.B.
Lounsbury, M.J.	Malterud, K.E.
Lueders, W.	Mal'tseva, S.P.
Luehrs, K.	Mamaev, V.P.
Lumbroso, H.	Manchanda, V.P.
Lundin, R.	Manecke, G.

Mani, R.	Mathur, K.B.
Mankiwala, S.C.	Mathur, K.B.I.
Manson, J.	Matsuda, A.
Mansour, A.K.	Matsukawa, S.
Maradufu, A.	Matsukuma, T.
Marathey, M.G.	Matsumoto, K.
Marchand, B.	Matsumura, K.
Marchand, J.	Matsuura, A.
Marchenko, I.G.	Matsuura, S.
Marchuk, L.A.	Matthes, A.
Margraf, H.W.	Matyas, G.
Maria Ada Jorio	Mauret, P.
Marini-Bettolo, G.B.	McCorkle, J.E.
Markham, E.C.	McElvain, S.M.
Markham, K.R.	McGhie, J.F.
Maroni, P.	McKillop, A.
Maroni-Barnaud, Y.	McGowan, J.C.
Marrian, D.H.	McLaughlin, J.A.
Marsman, B.	McMillan, J.A.
Martegiani, E.	McVeigh, J.L.
Martin, G.J.	Mebane, A.B.
Maruyama, M.	Medawar, G.
Marvel, C.S.	Mehra, H.S.
Mataise, J.	Mehta, G.
Mathur, A.K.	Meisenheimer, J.

Melanta, K.R.	Miocque, M.
Mel'nikov, N.N.	Miquel, J.F.
Melody, D.P.	Mirek, J.
Membery, F.	Misato, T.
Menger, F.M.	Misikova, E.
Merchant, J.R.	Misiti, D.
Merlini, L.	Misra, S.S.
Mermillod-Blardet, D.	Mitina, V.G.
Merrill, S.H.	Mito, K.
Merz, K.W.	Miyata, Y.
Messwarb, G.	Mizon, J.
Mester, T.	Mizuta, Y.
Metzger, J.	Moffat, J.
Metzner, A.	Mohapatra, P.K.
Meusel, W.	Mohapatra, S.N.
Meye, O.	Mokhtar, K.E.
Meyer, A.	Molodozhnikov, M.M.
Meyer, E.W.	Montaudo, G.
Meyer, F.J.	Monti, L.
Michael, A.	Mooney, B.
Michel, J.	Mori, K.
Mikhailov, B.M.	Morita, N.
Mikhailov, M.K.	Moriyama, A.
Mikhaleva, M.A.	Mors, W.B.
Miller, R.C.	Moskowitz, H.

Mott, L.	Nadkarni, D.R.
Moulton, W.N.	Nadkarni, S.M.
Moustafa, E.	Nagai, W.
Mueller, E.	Nagarajan, G.R.
Mueller-Enoch, D.	Nagura, T.
Mukaiyama, T.	Nagy, A.
Mukhedkar, A.J.	Naidu, R.R.
Mukherjee, B.	Naidu, R.S.
Mukherjee, N.	Naik, H.B.
Mulchandani, N.B.	Naik, V.G.
Muller, H.	Nakamura, T.
Munder, J.	Nakane, H.
Municio, A.M.	Nakanishi, M.
Munjai, R.C.	Nakaya, T.
Munzel, F.	Nakazawa, K.
Murakami, M.	Nanao, H.
Murphy, J.J.	Narasimhachari, N.
Murthy, A.K.	Nargund, K.S.
Murti, G.V.L.N.	Nasini, G.
Murti, V.V.S.	Natarajan, C.
Musgrave, W.K.R.	Naumenko, I.I.
Myers, P.L.	Navaro, J.
	Nayak, P.L.
	Nazarova, I.I.
	Neely, J.S.

Negreanu, P.A.

Nelson, J.F.

Nemec, P.

Nern, V.

Nesmeyanov, A.N.

Netter, R.

Neu, R.

Neubauer, A.

Neuhaus, L.

Neweihy, M.F.E.

Nielsen, B.J.

Nightingale, D.

Nikitchenko, V.M.

Nikitin, E.K.

Nikitina, A.N.

Nikonov, G.K.

Nikulín, V.N.

Nilsson, M.

Nishio, N.

Noamichi, N.

Nogradi, M.

Nohara, F.

Noltes, J.G.

Nomura, Y.

Normant, H.

Normington, J.B.

Norman, R.O.C.

Novelli, A.

Noyce, D.S.

Numerof, P.

Obara, H.

Oberheiden, H.

Oberholzer, M.E.

Obolentseva, G.V.

O'Brien, F.L.

O'Brien, K.G.

O'Brien, S.

O'Conneide, F.

Offe, H.A.

Oganesyan, E.T.

O'Grady, J.

Ohkura, K.

Okada, K.

Okada, S.

Okamoto, K.

Okorie, D.A.

Old, K.B.

Oleinik, A.V.

Oleinikova, T.A.  
Olekhnovich, E.P.  
Ollis, W.D.  
Omote, Y.  
Ono, F.  
Onodera, J.  
Ooshima, M.  
Orazi, O.O.  
Orlov, V.D.  
  
Ormand, K.L.  
Ornduff, R.  
Oroshnik, W.  
Osaki, M.  
Oshiro, S.  
Osipov, O.A.  
Osterburg, J.  
Osteux, R.  
Ostrovskaya, B.I.  
O'Sullivan, W.I.  
Ouma, J.H.  
Overholzer, M.E.  
Oyamada, T.

Pacheco, H.  
Packman, A.M.  
Packman, E.W.  
Padwa, A.  
Pak, V.D.  
Pakudina, Z.P.  
Palluel, A.L.L.  
Panasenko, A.I.  
Panda, S.P.  
Panouse, J.J.  
Parikh, S.R.  
Paris, M.  
Paris, R.  
Paris, R.R.  
Parkes, M.W.  
Parmar, V.S.  
Parnes, Z.H.  
Parthasarthy, M.R.  
Parthasarthy, P.C.  
Pascal, Y.L.  
Pascual-Vila, J.  
Pasternak, R.  
Pastuska, G.  
Patampongse, C.  
Patel, D.R.



Patel, C.C.	Pfliegel, T.
Patel, H.	Philbin, E.M.
Patel, S.R.	Phillips, P.H.
Patell, J.R.	Phillip's, N.V.
Patil, B.R.	Piccardi, G.
Patonay, T.	Pineau, J.P.
Patraik, A.K.	Pinegina, L.Y.
Patwardhan, B.H.	Pings, W.B.
Pauling, C.	Pinhey, J.T.
Paulson, M.C.	Piozzi, F.
Pederiva, R.	Piscope, E.
Pendse, H.K.	Pivnenko, N.S.
Pera, J.D.	Planinsek, H.J.
Pereyaslova, D.G.	Plati, J.T.
Perjessy, A.	Plekhotkina, M.M.
Perrot, R.	Plostinaru, S.
Perroud, F.	Podimuang, V.
Perry, M.	Podwinski, B.
Pete, J.P.	Pogonina, R.I.
Peterson, W.J.	Pohl, R.
Peterson, W.R.	Pointet-Guillot, M.
Petrov, V.A.	Polansky, O.
Petrovsky, P.V.	Pollard, C.B.
Petrowitz, H.J.	Polyakov, L.L.
Pfeiffer, P.	Pongratz, A.

Ponomarev, A.A.	Quast, L.
Ponsold, K.	
Popandova, K.V.	
Potashnikova, S.G.	Rabaron, A.
Pourrias, B.	Rabassa, R.J.
Praetorius, P.	Rabinovich, D.
Prasad, K.	Rabjohn, N.
Pratt, R.E.	Radeglia, R.
Prevost, C.	Radkova, S.S.
Price, D.	Rai, H.S.
Princhar, S.	Raiford, L.C.
Pristupa, V.K.	Raikova, T.S.
Pritze, P.	Rajagopal, S.
Profft, E.	Rajagopalan, D.
Prokof'ev, E.P.	Rajagopalan, S.
Prokopovich, V.P.	Rajunas, J.V. (Jr.)
Proksch, G.	Rakhimov, A.A.
Proskauer, S.	Rakosi-David, E.
Pryor, W.A.	Rakosi, M.
Puri, B.	Rall, G.J.H.
Purrello, K.	Ramakrishnan, G.
Pursglove, L.A.	Ramakrishnan, V.T.
Puseh, U.	Ramdas, K.
	Rangaswami, S.

Rao, J.M.	Reynolds, G.A.
Rao, K.V.J.	Riche, J.
Raouf, A.	Riley, T.
Rappoport, Z.	Rimpler, H.
Rasschaert, A.	Rinker, E.H. (Jr.)
Rathmal, W.G.	Rinow, A.
Raushal, A.	Ristic, S.
Raut, K.B.	Rizzi, G.P.
Raval, A.A.	Robas, V.I.
Raven, P.H.	Roberman, A.I.
Ray, L.P.K.	Robert, J.F.
Raynaud, G.	Roberts, A.
Razak, S.	Roberts, J.D.
Real, L.	Roberts, R.J.
Reddelien, G.	Robertson, G.H.
Redman, B.T.	Robertson, P.W.
Regode Sousa, J.	Roblin, B.
Reichel, L.	Rochard, J.C.
Reilly, J.	Rochlitz, S.
Reimann, E.	Rochus, W.
Reinhardt, M.	Romono, C.
Reinprecht, L.	Rorig, K.J.
Reis, E.	Rose, J.D.
Rembold, H.	Rosenberg, A.
Reuter, F.H.	Rosenberg, S.D.

Roshka, G.K.

Ross, J.

Rossbach, G.

Rossi, G.V.

Rothbaum, H.P.

Rousselet, R.

Rout, M.K.

Rout, N.

Roux, D.G.

Row, L.R.

Roy, D.N.

Rozum, Y.S.

Rublin, N.

Ruchkin, V.E.

Ruckert, H.

Ruiz, E.B.

Ruiz, J.L.

Rumberger, G.G.

Rumyantsev, N.P.

Rumyantseva, K.S.

Rusina, A.

Russell, A.

Russell, P.B.

Ryaboi, V.M.

Rybin, L.V.

Rybinskaya, M.I.

Ryerson, G.D.

Ryvolova-Kejharova, A.

Saad, S.F.

Sabata, B.K.

Sachs, G.

Sadykov, A.S.

Saffer, C.M. (Jr.)

Sah, P.P.T.

Saha, A.K.

Saied, F.

Saigo, K.

Saitoh, T.

Saiyad, I.Z.

Sakaguti, T.

Sakakibara, M.

Sakharova, N.A.

Sakurai, Y.

Salagar, S.S.

Saleh, N.A.M.

Salem, M.A.

Sallai, J.

Sallay, P.

Salvadori, P.	Sazonova, V.A.
Sammes, P.G.	Schächer, F.
Sammour, A.	Scheinmann, F.
Sammour, A.A.	Schellenberg, W.D.
Sammour, A.E.A.	Schettino, O.
Sammour, A-M. A.	Scheur, P.J.
Samokhvalov, G.I.	Schickle, R.
Samour, A.A.	Schill, L.
Samsonov, V.A.	Schilling, C.
Samula, K.	Schloegl, K.
San, T.	Schmidt, F.
Santiago, M.	Schmidt, G.M.J.
Sanyal, A.K.	Schmidt, H.
Sasaki, S.	Schoenecker, B.
Sasson, Y.	Scholtis, K.
Sathe, S.W.	Schommer, W.
Sato, S.	Schraufstätter, E.
Satpathi, P.S.	Schroeder, O.C.
Satpathy, K.K.	Schroll, G.
Savin, V.I.	Schuchhardt, W.
Sawada, I.	Schuetz, G.
Sawicki, E.	Schwyzer, A.
Saxena, M.K.	Scott, F.L.
Sayed, A.A.	Scott, G.P.
Sayles, D.C.	Scrocco, M.

Sedova, V.F.

Seedorf, C.

Seguin, J.P.

Seikel, M.K.

Seki, T.

Selezneva, E.A.

Selim, M.

Selim, M.I.B.

Selim, S.F.

Selvaraj, Y.

Semenov, A.I.

Serbin, A.G.

Sergant, M.

Sergi, G.

Serum, J.W.

Servi, S.

Seshadri, S.

Seshadri, T.R.

Seter, J.

Setsu, M.

Seyffert, W.

Seyfried, M.

Seyler, J.K.

Shagidullin, R.R.

Shah, D.N.

Shah, N.J.

Shah, N.M.

Shah, P.R.

Shah, R.V.

Shakhova, M.K.

Shakked, Z.

Shamshurina, S.A.

Shanbhag, M.N.

Shanmuganathan, S.

Sharma, A.

Sharma, D.K.

Sharma, G.C.

Sharma, P.

Sharma, R.C.

Sharma, R.P.

Sharma, S.D.

Sharma, T.C.

Sheinkman, A.K.

Shelepin, O.E.

Shelepina, V.L.

Shenoi, B.B.

Sheradsky, T.

Sherif, O.

Sherman, G.P.

Shi, J.Y.	Silver, N.L.
Shibata, S.	Silvestri, S.
Shibata, Y.A.	Simalty, M.
Shima, G.	Simon, Y.
Shimokoriyama, M.	Simonova, E.V.
Shinoda, J.	Simpson, T.H.
Shinkarenko, A.L.	Singer, J.
Shinokawa, H.	Singh, A.
Shintomi, K.	Singh, A.K.
Shkumat, A.P.	Singh, R.K.
Shotter, R.G.	Singh, V.K.
Shozda, R.J.	Singhal, D.V.
Shriner, R.L.	Sinyagovskaya, L.A.
Shuichi, H.	Sipos, G.
Shukla, Y.N.	Sirokman, T.
Shul'pin, G.B.	Sjöstrom, E.
Shur, A.M.	Skrigan, A.I.
Shur, I.A.	Smirnova, G.A.
Shvetsova-Shilovskaya, K.D.	Smith, D.M.
Shyrina, V.M.	Smith, H.E.
Sib, S.	Smith, J.H.
Siddall, W.	Smith, L.I.
Siemiatycki, M.S.	Sm'olentseva, L.G.
Silhan, W.	Sohar, I.
Silva, M.	Sokoloff, B.T.

Sokolov, N.A.	Stenlid, G.
Solomonovici, A.	Stepanov, B.I.
Somerfield, G.A.	Stepanova, G.P.
Sonaware, H.R.	Stephens, W.D.
Soni, V.T.	Steppan, H.
Sood, G.R.	Stewart, V.E.
Sorrie, A.J.S.	Stobbe, H.
Souchay, P.	Stockx, J.
Soussan, G.	Stoilov, L.
Southwick, P.L.	Stonehill, H.I.
Spacu, P.	Strat, G.
Spasov, S.L.	Strat, M.
Specht, D.P.	Streigler, C.
Stanek, J.	Strelisky, J.
Stankoviansky, S.	Struharova, L.
Stanley, W.L.	Studinger, H.
Star, A.E.	Stysenko, T.S.
Stark, H.	Su, J-T.
Starkov, S.P.	Subbarao, B.C.
Starkova, S.K.	Subrahmanyam, K.
Staudinger, H.	Sudgen, J.K.
Stecher, H.	Sugihara, Y.
Stefanovskii, Y.N.	Sugiyama, K.
Steinhofer, A.	Sugiyama, N.
Stendel, J.	Sukach, Y.A.



Sukhorukov, A.A.  
Sunshine, N.B.  
Suri, S.C.  
Surov, Y.N.  
Suschitzky, H.  
Sutherland, I.O.  
Sutherland, R.G.  
Suzuki, K.  
Swamer, F.M.  
Swann, B.F.  
Swett, L.R.  
Swirski, J.  
Sword, I.P.  
Sy, M.  
Syamasundar, K.  
Szabo, G.B.  
Szamant, H.H.  
Szejtli, J.  
Szell, T.  
  
Szent-Gyorgyi, A.  
Szigeti, P.  
Szucs, L.  
Szymanski, S

Taft, W.K.  
Takagi, S.  
Takahashi, H.  
Takatori, M.  
Takayanagi, Y.  
Takeshita, K.  
Tambor, J.  
Tanaka, I.  
Tanaka, J.  
Tanasescu, I.  
Tandon, J.S.  
Tanghe, L.J.  
Taran, L.A.  
Tarbell, D.S.  
Tarburton, P.  
Taschek, R.F.  
Tatsuta, H.  
Tatuta, H.  
Taylor, E.C.  
Taylor, H.M.  
Taylor, M.D.  
Telenyl, Mrs. P.  
Tetenbaum, M.T.  
Teuber, H.J.  
Tewari, R.P.

Tewari, S.S.	Todd, A.R.
Thakkar, G.P.	Todd, J.
Thakor, V.M.	Tokes, A.
Thomas, F.	Tokes, A.L.
Thomas, J.F.	Tolmachev, V.N.
Thomas, M.	Tolmachov, V.M.
Thomas, M.B.	Toma, S.
Thomassery, P.	Tomas, F.
Thomassery, V.	Tomeufcik, A.S.
Thompson, D.T.	Torrance, S.J.
Thompson, R.B.	Trakroo, P.P.
Thomson, R.H.	Trapp, V.
Thuy, N.M.	Treblow, M.D.
Thyagarajan, G.	Tricozzi, C.
Timmons, C.J.	Tripathi, R.D.
Timoney, A.	Trippett, S.
Ting, I.	Trieu, T.C.
Tinland, B.	Trivedi, J.P.
Tirouflet, J.	Trivedi, P.L.
Tischenko, V.G.	Tröltzsch, C.
Tischenko, V.N.	Truett, W.L.
Titov, E.N.	Trummer, I.
Tivey, D.J.	Trusevich, N.D.
Tjakob, H.J.	Tryon, M.
Toba, K.	Tsjuji, A.

Tsuchiya, C.	Vais, A.L.
Tsuda, A.	Vakharia, M.N.
Tsukamoto, M.	Van Allan, J.A.
Tsukerman, S.V.	Vander Merwe, J.P.
	Van De Sande, C.
Tsukervanik, I.P.	Vandewalle, M.
Tsuruta, T.	Vandrewalla, H.P.
Tucker, S.H.	Van Sen den, K.G.
Turov, A.V.	Van Stone, A.E.
	Varnai, I.
	Vasilevich, I.F.
	Vassort, P.
Uchiyama, H.	Velarde, E.
Udupa, S.R.	Venetz, J.
Ukai, S.	Veng, T.
Umirzakov, B.	Venkataraman, K.
Unicler, S.A.	Venturella, P.
Uno, J.	Veres, K.
Uno, K.	Vereshchagin, A.N.
Unruh, C.C.	Verkhovod, N.N.
Unterhalt, B.	Verkhovod, V.M.
Uong, T.	Verma, B.L.
Uragg, H.	Vermenichev, S.M.
Uri, N.	Vernekar, S.S.
Utenkova, G.N.	Verzele, M.
Uzan, R.	

Viel, C.  
Vieregge, H.  
Villard, C.  
Vinokurov, I.I.  
Vkai, S.  
Vladimirov, Y.A.  
Vlasov, V.G.  
Vodzinskiĭ, Y.V.  
Vogel, J.J.  
Volbushko, N.V.  
Volke, J.  
Volkotrub, M.N.  
Volland, H.  
Volovik, A.M.  
Volpers, F.  
Volsteedt, F. du R.  
Vorländer, D.  
Vorobeva, R.P.  
Voronkin, V.M.  
Vorontsova, L.G.  
Vul'fson, S.F.  
Vyas, G.N.

Wacek, A.V.  
Wadodkar, P.N.  
Wadsworth, W.S. (Jr.)  
Wagh, S.P.  
Wagner, H.  
Walker, D.M.  
Walker, E.A.  
Walker, G.  
Wall, L.A.  
Walsh, W.L.  
Walter, H.  
Wang, E.  
Wang, S.C.  
Wang, S.M.  
Warnowius, H.  
Warwick, H.  
Warriar, A.M.  
Watanabe, M.  
Watanable, T.  
Watson, W.R.  
Wawzonek, S.  
Weber, F-G.  
Weber, W.  
Weichselbaum, T.E.  
Weidlich, H.A.

Weiner, N.	Williams, D.
Weissenboeck, G.	Williams, D.H.
Weitz, E.	Williams, J.L.R.
Weizmann, C.	Wilson, C.L.
Welcomme, N.	Wilson, C.V.
Welstead, W.J. (Jr.)	Wilson, C.W.
Wender, S.H.	Wilson, F.J.
Wermuth, C.G.	Wilson, R.H.
Westphal, G.	Winternitz, F.
Weygand, C.	Wittig, G.
Weygand, P.	Wittman, H.
Whalley, W.B.	Woelm, F.M.
Wheeler, O.H.	Wofner, A.
Wheeler, T.S.	Wolf, E.
White, D.E.	Wolf, V.L.
White, T.	Wolfner, A.
Whiting, D.A.	Wolinski, J.
Widdows, S-T.	Wollenweber, E.
Wiedhopf, R.M.	Wolpa, L.I.
Wienert, L.A.	Wolstenholme, W.A.
Wiermann, R.	Woo, G.L.
Wiles, Q.T.	Woodham, A.A.
Wiley, R.H.	Woods, G.F.
Wilkinson, R.G.	Woodward, R.B.
Williams, A.E.	Woolenweber, E.

Worm, G.  
Worrall, D.E.  
Wrang, P.  
Wright, G.F.  
Wright, J.C.  
Wu, T.S.  
Wurm, G.  
Wyar, T.  
Wynberg, H.  
  
Xicluna, A.  
Xuong, N.D.  
  
Yakovlev, I.P.  
Yamada, S.  
Yamaguchi, H.  
Yamaguchi, K.  
Yamaguchi, M.  
Yamamoto, C.  
Yamamoto, S.  
Yamamura, K.  
Yamanaka, K.  
Yamato, M.  
  
Yan, C-F.  
Yang, N.C.  
Yanovskaya, L.A.  
Yarkovlev, L.K.  
Yaroslavsky, S.  
Yasuda, Y.  
Yates, P.  
Yatsenko, A.I.  
Yatsevich, N.M.  
Yavorskaya, G.M.  
Yokomori, S.  
Yokoyama, K.  
Yokoyama, T.  
Young, A.N.  
Young, J.R.  
Young, J.T.  
Young, W.G.  
Yuldashev, K.Y.  
Yuldasheva, L.K.  
Yur'ev, Y.K.  
Yuwiler, A.

Zadorozhnyi, B.A.  
Zaher, H.A.  
Zahir, S.A.  
Zahir, S.A.C.  
Zahradn'ik, P.  
Zalukaev, L.P.  
Zapesochnaya, G.G.  
Zarandy, M.S.  
Zech, K.  
Zinn, M.F.  
Zolotarev, B.M.  
Zorina, T.M.  
Zsolnai, T.  
Zuffanti, S.  
Zugrăvescu, I.  
Zuman, P.

Subject Index

Acetone cyanohydrin

Acetophenone

o- and p-Acetoxybenzoic acid

o-Acetoxychalcones

2'-Acetoxychalcone  $\alpha$ ,  $\beta$  -dibromides

2'-Acetoxychalcone  $\alpha$ ,  $\beta$  -dichlorides

Acetylacetone

6-Acetyl-5,8-dihydroxy-2,2-dimethoxychromene

Acrylate-styrene copolymers

Acrylyl chloride

Acyl carbenes

1,2-addition

1,4-addition

Adhesives

Air degradation

Aliphatic nitriles

Alkali metal borohydride

Alkali sulphide

Alkaline hydrogen peroxide

Alkaline hydrogen peroxide oxidation

Alkaloids

Alkylation

Allyl alcohols



Alumina

Aluminium chloride

Aluminium chloride-sodium chloride

Aluminium isopropoxide

Amberlite

Amidines

Amidine-hydrochloride

1,2-Amino alkoxychalcone and its acid addition salt

Aminoazachalcone

$\omega$ -Aminobenzenethiol

$\alpha$ -Aminochalcone

4- (and 4'-) aminochalcone

1-Amino-1,3-diphenyl-3-propanol

2-Aminoethanethiol

Aminoflavanone

4-Aminohalogenochalcone

Amino magnesium compound

Ammonia-amalgam

Ammonium sulphide

Amorphigenin

Analytical reagents

Anhydrous aluminium chloride

Aniline

$\beta$ -Aniline-benzylacetophenone

Anthocyanin

Anti-conformation

Anti-S-cis conformer

Antimony pentachloride

Antimony pentachloride test

Antioxidants

Apigenin

Aromatic acids

Aromatic L-amino acid carboxylase

Aromatic thioamides

trans-1-Aryl-2-aroxyloxyethylene

Aryl benzyl ethanolamines

$\beta$ -Arylchalcone

Aryl copper

Aryliodine

2-Aryl quinolines

Arylselenols

2-Aryl-1-tetralone

Arylidene bis urea

Asebotin

Aspirin

Aurones

Aurone, cis- and trans

Autoxidation

Azafluorenones

Azepine derivatives

$\Delta$ -Azidochalcone

Aziridine

Azoles

Basicity

Bathochromic shift

Beckmann rearrangement

Benzalacetone

Benzalacetophenone

Benzaldehyde

3-Benzomido-3-phenylpropiophenone

Benzenethiol

Benzofuranones, diastereoisomeric

Benzoic acid

Benzoic acid, substituted

Benzils

5,6-Benzochromanones, substituted

Benzophenone

Benzoins

Benzonitrile

2-Benzhydryl-3-hydroxy-3, $\beta$ -diphenyl propionic acid

Benzhydryl sodium

Benzoyl acetic ester

Benzoyl chloride

Benzoyl coumarone

3-Benzoyl-4-keto-1,2,6-triphenylcyclohexane nitrile

$\alpha$ -Benzoyl- $\beta$ -phenylcyclopentanoylethane

$\alpha$ -Benzoyl- $\beta$ -phenyl-3-methylcyclohexanoylethane

2-Benzoyl-3,4,6-triphenyl-2,3-dihydropyran

$\beta$ -Benzoyloxy-2'-hydroxychalcone

Benzylacetophenone

Benzylamine

Benzyl-p-tolyl sulphone

Benzylic carbonium ion

Benzylidene acetophenone

Benzylidene bis acetophenone

2'-Benzyloxychalcone dibromide

2'-Benzyloxychalcone epoxide

2'-Benzyloxy-4,4'-dimethoxy chalcone

2'-Benzyloxy-4-methoxychalcone epoxide

2'-Benzoyloxy-4-methoxy- $\alpha$ -hydroxy- $\beta$ -ethoxy dihydrochalcone

1-(2-benzyloxyphenyl)-2-hydroxy-3-chloro (p-methoxyphenyl)-propan-1-one

Berberine

Betaine like methylene triphenylphosphorane

Bicyclic analogue of chalcone

Bicyclic keto alcohol

Bimolecular compounds

Bimolecular products

Bis adduct

4,4'-bis (diphenylamino) chalcone  
N,N-bis ( $\alpha$ -phenacylbenzyl) methylamine  
Boron trifluoride  
Brockmann's alumina  
Bromination, nuclear  
Bromine addition to chalcone, kinetics of  
Bromine chloride  
Bromine fluoride  
 $\alpha$ -Bromochalcone  
 $\beta$ -Bromochalcone  
4'-Bromochalcone  
3-Bromo-2'-nitrochalcone  
4-Bromo-2'-nitrochalcone  
 $\alpha$ -Bromo- $\beta$ -ethoxychalcone  
 $\alpha$ -Bromo- $\beta$ -methoxychalcone  
 $\alpha$ -Bromo- $\beta$ -methoxy- $\beta$ -phenyl propiophenone  
 $\alpha$ -Bromo- $\beta$ -propoxychalcone  
trans- $\alpha$ -Bromomethylchalcone  
1-Bromo-2-methyl-2-imidazoline  
N-Bromomorpholine  
N-Bromosuccinimide  
Butein  
Butin  
Tert. butyl hydroperoxide  
n-Butyl magnesium bromide  
Butyric ester

Calcium hydride

Camphor

4- Carbethoxychalcone

$\alpha$ -Carbethoxy- $\beta$ -phenyl- $\gamma$ -benzoyl butyric ester

Carbinol

Carbocyanine dyes

Carbonium ion

Carbon monoxide

Carbonyl stretching frequency

Carbonyl ylides

Carboxychalcones

Carboxylic acid derivative of chalcones

Catalysed oxidation

Catalytic hydrogenation,  $\text{PtO}_2$

Chalcol

Chalcone

Cis-chalcone

trans-chalcone

Chalcone analogues of:

Acridine

Anthracene

Benzochrotrone

1,4-Benzodioxans

Caffeic acid

Carbazole

Cymantrene

Ferrocene

Furan

8-Hydroxyquinoline

Indole

Naphthalene

Phenanthrene

Piperidine

Pyrazole

Pyridine

Pyridone

Pyrrole

Quinoline

Selenophene

Thiophene

Chalcone complexes (1:1)

Chalcone complexes with antimony pentachloride

boric acid

ferric chloride

Chalcone derivatives

Chalcone  $\alpha$ ,  $\beta$ -dibromides

Chalcone  $\alpha$ ,  $\beta$ -dichlorides

Chalcone  $\alpha$ ,  $\beta$ -dichlorides, stereoisomeric

Chalcone dimers

Chalcone-2,4-dinitrophenylhydrazone

t-Chalcone epoxide  
t-Chalcone epoxide, absolute configuration of,  
Chalcone-flavanone isomerase  
Chalcone glucoside  
Chalcone glycoside  
Chalcone hydrosulphide  
Chalcone-metanil indicator  
Chalcone oxime, trans.  
Chalcone syn-oxime  
Chalcone phenylsemicarbazone  
Chalcone semicarbazone  
Chalcone sulphonamide  
Chalcone sulphonic acid  
Chalcone thiosemicarbazone  
Chalcononaringenin-4-glucoside  
Chalols  
Chelation  
Chiral crystals  
Chlorine  
Chlorine thiocyanate  
 $\alpha$ -Chlorochalcone  
4-Chlorochalcone  
2'-Chlorochalcone  
4'-Chlorochalcone  
5-(4-Chlorocinnamoyl) salicylic acid



2'-Chloro-4,4'-difluorochalcone  
6-Chloro-1,3-dihydroxy-2-phenylquinolin-4 (1H)-one  
Chlorohydrin  
Chlorohydroxychalcone  
4-Chloro-4'-hydroxy-5'-carboxychalcone  
 $\alpha$ -Chloro- $\beta$ -methoxy- $\beta$ -phenylpropiophenone  
4-Chloro-5'-methyl-2-thioalkyl chalcone  
3-Chloro-2'-nitrochalcone  
N-chlorosulphonyl-4,6-diphenyl-2-oxo-3,5-dihydro-1,3-oxamine  
Chlorosulphonylisocyanate  
Cholinesterase  
Chromanones  
Chromenes  
Chromenochalcone  
Chromic acid  
Chromogenic reagent  
Chromophoric group  
Chromous chloride reduction  
Chromous salt  
Chrysene  
Chrysin  
Cinnamic acid, substituted  
Cinnamoyl chalcone  
5-Cinnamoyl salicylic acid  
Cinnamoylidene acetophenone

4-Cinnamylidene-2,5-cyclohexadien-1-one  
Cisoid conformation  
Claisen-Schmidt reaction  
Cleavage of C<sub>1</sub>-C<sub>2</sub> oxirane bond  
Cleavage reaction  
Clemmensen reaction  
Cobalt chloride  
Column chromatography  
Colour photography  
Colour reaction  
Complex metal hydride  
Complexing action of 2,2'-hydroxychalcone on Sn (IV) salts  
Complexometric titration  
Condensing agents  
    Aluminium chloride  
    Aqueous alkali  
    Boron trifluoride  
    Hydrogen chloride  
    Piperidine  
    Sodium methylate  
Conductometric method for the estimation of copper  
Conformation  
Conjugate addition  
Conjugation  
Cordoin

Coumaran-3-one  
Coumarinochalcone  
Coumestrol  
Cross bromination products  
Cross linking agents  
Crystallography  
Cuprous chloride  
Cyanoacetamide  
Cyanocobalt complex  
1-Cyano-2-methyl-2-aminoethylene  
Cyanomethylchalcone  
3-Cyano-4-phenyl pyridine  
Cyclisation  
Cyclisation of 2'-hydroxychalcone epoxide  
Cycloaddition  
Cyclodextrin  
Cyclohexylamine-iodine complex  
trans-1-Cyclohexyl-2-phenyl-3-benzoylethylene-immine  
Cyclopentanone  
Cyclopropane derivative  
Cyclopropenes, substituted  
Cystein

Darzen's condensation  
Davidigenin and 4'-methoxy derivative  
Davidioside  
Deacetylation  
Debromination  
Decarbethoxylation  
Degradation  
Dehydration  
Dehydrobromination  
Dehydrochlorination  
Dehydrohalogenation  
Demethylation, partial  
Deoxybenzoin  
Derricidin  
Derricin  
Deuterium isotope  
Dialkylamino alkoxy derivative of chalcone  
 $\alpha, \beta$ -Diaminobenzylacetophenone  
3,5-Diaryl-4-hydroxy- $\Delta^2$ -pyrazoline  
Diastereoisomeric diketones  
Diazomethane  
Dibenzalacetophenone disulphide  
Dibenzaltriacetophenone  
1,4-Dibenzoyl-2,3-diphenylbutane  
Dibenzoylmethanes

Dibenzyl diacetophenone

2,5'-Dibromochalcone

4,4'-Dibromochalcone

3,5-Dibromo-2,2'-dihydroxychalcone

1,3-Dibromo-5,5'-dimethylhydantoin

4',5-Dibromo-2-hydroxychalcone

N,N-Dibromosulphonamide

Dibutyl ether

4,4'-Dichlorochalcone epoxide

Dichloroethane

2,4-Dichlorophenoxyacetic acid

Dicyclohexylpropane

3',7-Diethoxy-2',4'-dimethoxyisoflavone

Diethylamine

2-Diethylaminoethyl mercaptan

3-Diethylaminopropyl mercaptan

1,1-Diethylamino-prop-1-yne

1,1-Diethyl-2-benzoyl-3-phenylcyclobutane

Diethyl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate

(see Hantzsch Ester)

3',7-Diethoxy-2',4'-dimethoxyisoflavone

9,10-Dihydroanthracene

Dihydrochalcone

Dihydrochalcone galactoside

Dihydrochalcone xyloside

Dihydroisoxazole

Dihydro pyrazole

Dihydro resorcinol

4',6-Dihydroxyaurone

2',4-Dihydroxy-3,5-tert. butylchalcone

3,4-Dihydroxy-3'-carboxychalcone

Dihydroxychalcone

2,2'-Dihydroxychalcone

2,4-Dihydroxychalcone

3,4-Dihydroxychalcone

4,4'-Dihydroxychalcone

2',3-Dihydroxychalcone

2',4'-Dihydroxychalcone

2',4'-Dihydroxy-dihydrochalcone

2',4'-Dihydroxy-3',6'-dimethoxychalcone

2',4'-Dihydroxy-4',5'-dimethoxychalcone

4',7-Dihydroflavanone

4',7-Dihydroflavonol

2',4'-Dihydroxy-3-methoxychalcone

2',4'-Dihydroxy-6-methoxychalcone

2',6'-Dihydroxy-4'-methoxy-3,5'-dimethyl dihydrochalcone

4,4'-Dihydroxy-2'-methoxychalcone

2',6'-Dihydroxy-3'-methyl-4'-methoxychalcone

Dihydroxy phenylalanine carboxylase

2,2'-Dihydroxy-3,5,5'-tribromochalcone

2',4-Dihydroxy-4',5',6'-trimethoxychalcone

Diketones

Dimeric monocarboxylic acid

Dimerides

Dimerisation

Dimers

2,4-Dimethoxybenzoic acid

4,4'-Dimethoxy chalcone

4,4'-Dimethoxy chalcone epoxide

4,4'-Dimethoxy- $\beta$ -hydroxychalcone

Dimethyl acetylene diacboxylate

4-Dimethylaminochalcone

2-(2-dimethylaminoethoxy) chalcone

2-(2-dimethylaminoethoxy)3',4',5'-trimethoxy-chalcone  
hydrochloride

4-Dimethylamino chalcone

$\alpha$ -Dimethylaminophenyl acetonitrile

4,4'-Dimethylchalcone

5,5'-Dimethylcyclohexan-1,3-dione

3,5-Dimethyl-4-nitroisoxazole

(+)-di-O-methyl pinobankin

Dimethyl sulphonium methylide

Dimethyl sulphoxonium methylide

gem-Dinitroalkane

2,4-Dinitrophenylhydrazine

2,4-Dinitrophenylsemicarbazide

## Dioxoles

3,5-Diphenyl-1-acetamido-2-pyrazoline

4-Diphenyl aminochalcone

2,4-Diphenyl-6,7-benzo-1-thia-5-aza-4,6-cycloheptadiene

Diphenyl beryllium

2,4-Diphenyl-5 (or 1)-isopropyl-8 (or 6) methyl-9-keto-4-hydroxy-bicyclononane

3,5-Diphenylisoxazoline

Diphenyl ketene quinoline

Diphenyl mercury

 $\alpha$ ,  $\alpha'$ -Diphenyl- $\beta$ -methoxyphenyl- $\gamma$ -benzoyl-butyric ketone

1,3-Diphenyl-3-(2-nitro-1,3-indandion-2-yl)-1-propanone

1,3-Diphenyl-1,2-propandiol

1,3-Diphenylpropane

1,3-Diphenylpropanol

1,3-Diphenyl-1-propanol

1,3-Diphenyl-2-propanol

1,3-Diphenyl-prop-1-ene

1,3-Diphenyl-2-propen-1-ol

1,3-Diphenyl-propen-1-one

 $\beta$  -  $\beta'$ -Diphenylpropiophenone (3,3-Diphenyl propiophenone)

1,3-Diphenyl propyl alcohol

1,3-Diphenyl-1-propyn-3-one

3,5-Diphenyl-1-pyrazoline

Diphenyl styryl carbinol

3,5-Diphenyl-1-thioacetamido-2-pyrazoline



.phenyl tin hydride  
.pole moment  
.3-Di (2-pyrryl) propenone  
.ol  
.sproportionation  
.sodiophenone  
,N-Disubstituted-2-( $\omega$ -aminoalkoxy)-3',4',5'-trimethoxychalcone  
opping mercury electrode  
rnone  
rpinacol

Electrode reduction  
Electrolytic reduction  
Electron bombardment  
Electronic absorption spectra, heterocyclic chalcone analogues  
Electrophotographic products  
Electrophilic attack  
Electrophilic hydroxylating system  
sol tautomer  
enzymatic transformations  
oxidation  
oxide ring opening, mechanism of  
oxy resins  
equilibrium

Eriodictin

Erythro and threo

Erythro chalcone dihalides

$\beta$ -Ethoxy chalcone

2-Ethoxy chalcone

2-Ethoxyflav-3-one

Ethyl acetoacetate

Ethyl- $\alpha$ -acetyl- $\beta$ -phenyl- $\gamma$ -benzoyl-butyrate

Ethyl alkyl malonate

Ethyl benzoyl acetate

p'-Ethylchalcone

Ethyl cyanoacetate

Ethyl- $\alpha$ -cyanobutyrate

Ethyl- -cyano- $\beta$ - $\gamma$ -diphenylbutyrate

Ethyl magnesium bromide

Ethyl phenyl acetate

Ethyl thioglycolate

Ethylene diamine tetraacetic acid

Ethylene glycol

Ethylene imine ketone

Ethynyl carbinol

Eutectic

Extinction coefficient

Fenchone

Ferric chloride

Ferrocene analogue of chalcone

Ferrous sulphate

Flavan

trans-2,3-cis-3,4-flavandiol

Flav-3-ene

Flavanols

Flavanones

Flavanonols

Flavone

Flavones

Flavonoid biosynthesis

Flavonoids

Flav-3-ol

Flavanols

Flavylium salts

Flemi-chapparin-A

Fluoboric acid

Fluorescence

Fluorescence, quenching of

Fluorescent adsorbent

Fluorescent whitening agent

Fluorometric method

2-Fluoro-3-nitro-4-chalconyl-6-phenyl-acetamido penicillanate

Formation constant  
Friedel Crafts alkylation  
Fries migration  
Furan analogues of chalcone  
ω -Furfuylacetophenone

Gauche conformation

Geometric isomerism

Geometric isomers

Grignard reagents

Ground state

Halochromic effect

Haloform type cleavage

Halogenation

Halogenation, nuclear

Hammett constant

Hammett substitution constant

Hantzsch ester (see Diethyl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate)

Hantzsch-Werner hypothesis

Hesperidin

Hesperidin chalcone

Hesperidin dihydrochalcone glucoside

Hesperidin methylcarboxychalcone  
Hesperidin methyl chalcone  
Hesperatin chalcone  
Heterocyclic analogue of chalcone  
Heterocyclic epoxychalcones  
Hexyl resorcinol  
Homoflemingin  
Homogeneous hydrogen transfer  
Homologation of chalcone  
Hop extract  
Horse raddish peroxidase  
Huckel's molecular orbital method  
Huckel molecular orbital calculation  
Hydrazine  
Hydrazoic acid  
Hydrazone  
Hydride ion acceptor  
Hydrochalcals  
Hydrocyanic acid  
Hydrogen  
Hydrogen bonding, intermolecular and intramolecular  
Hydrogen bromide, in the presence of oxygen  
Hydrogen chloride in ether  
Hydrogen donor  
Hydrogen peroxide

Hydrogen peroxide, alkaline

Hydrogen sulphide

Hydrogenation, catalytic

Hydrogenation (Palladium-carbon catalyst)

Hydrogenation, selective

Hydrogenolysis

Hydrostannation

2-Hydroxyacetophenone

p-Hydroxybenzaldehyde

Hydroxybenzalcoumaranone

p-Hydroxybenzoic acid

2(o-Hydroxybenzoyl)-1-phenylethane sulphonic acid

2'-Hydroxy-3'-bromo-4,6'-dimethoxy chalcone

2'-Hydroxy-3'-bromo-4-methoxy-5'-methylchalcone oxime

2-Hydroxy-4-n-butoxy acetophenone

2'-Hydroxy-4'-carbethoxychalcone

4'-Hydroxy-5-carbethoxychalcone

2-Hydroxy-2'-carboxylic chalcone

Hydroxychalcones

Hydroxychalcone glycoside

3-Hydroxychalcone

o-Hydroxychalcones

cis-2-Hydroxychalcones

trans-2-Hydroxychalcone

o-Hydroxychalcone  $\alpha, \beta$  -dibromide

2'-Hydroxy chalcone

2'-Hydroxychalcone sulphonic acid

~~2~~ -Hydroxychalcone

~~2~~ -Hydroxychalcones

4'-Hydroxychalcone

4-Hydroxy cordoin

4-Hydroxy derricin

4'-Hydroxy-3',5'-diiodo-4-propoxy (and 4-butoxy) chalcone

2'-Hydroxy-4',6'-dimethoxychalcone 4-glucoside

2-Hydroxy-3,4-dimethoxy-3',4'-methylenedioxy chalcone

2'-Hydroxy-4',6'-dimethoxy chalcone

2'-Hydroxy-4',6'-dimethoxy-3'-methyl dihydrochalcone

2'-Hydroxy-4-dimethylaminochalcone

2'-Hydroxy-3',5'-dimethylchalcone

2-Hydroxy-4-n propoxy-5-nitroacetophenone

2'-Hydroxy-4',6',3,4-tetramethoxychalcone

Hypsochromic effect

Indenes

Indole-acetic acid oxidase

Indole-analogue of chalcone

Indoles

Inductive effect

Infra red

Infra red spectroscopy

Intermolecular complexes

Iodine complexes with amine

Iodine monochloride

Iodine thiocyanate

3-Iodo-6,8-dimethylflavanone

Ion exchange chromatography

Ionization potential

Ionization radiation

Iron carbonyl complexes

Iron tetracarbonyl

Iron tricarbonyl

Isobutyl ketone

Isocordoin

Isocyanatochalcone

Isoflavone

Isoliquiritigenin (2',4,4'-trihydroxychalcone)

cis-trans isomerism

Isonicotinic acid hydrazide reagent

Iso-octane

Isopentenyl chalcone

$\beta$ -Isopropoxychalcone



Isopropyl alcohol

Isopropyl ketone

Isosalipurposide

Isothiocyanato chalcone

Isoxazole

Isoxazoline derivative

Keto acetal

Keto aldehyde

Kinetics and mechanism of cyclisation of 2'-hydroxychalcone  
epoxide

Lacquers

- Lactone

$\delta$ -Lactones

Lead dioxide

Lead tetraacetate

Leuckart reaction

Limonene

Lipid membrane

Lipoid material

Liquiritigenin

Lithium acetylide

Lithium aluminium hydride-aluminium chloride

Lithium aluminium hydride reduction

Lithium amalgam

Lithium amide

Lucurzid

Luteolin

Magnesium carbonyl

Malonamide

Malonic ester

Manganic acetate

Mass spectrometry

Maximum rate of crystallisation

Mechanism of chalcone formation; base catalysed and acid catalysed

Mecinarone

Meerwein-Pondorf-Verley reduction

Menthone

Mercury cathode

Mesophase

Methacryloyloxychalcone

Methoxyamine

3-Methoxyaminopropiophenone

4-Methoxyaurone

1-(2-Methoxybenzoyl)-2-phenyl ethylene chlorohydrin

2-Methoxychalcone

cis-3-Methoxychalcone  
 2-Methoxychalcone epoxide  
 4-Methoxychalcone  
cis-4-Methoxychalcone  
 4'-Methoxychalcone  
 Methoxychalcones  
 $\beta$ -Methoxychalcone  
 4-Methoxy-2,4'-dibenzoyloxychalcone epoxide  
 4-Methoxy-4'-hydroxy-5'-carboxy dihydrochalcone  
 $\beta$   $\beta$ '-Methoxyimino bis-propionophenone  
 2'-Methoxy methoxychalcone  
 2'-Methoxymethoxy chalcone epoxide  
 2'-Methoxymethoxy-4',6'-dimethoxychalcone  
 $\beta$  -Methoxy-p'-methoxy-p-nitrochalcone  
 6'-Methoxy-6'-tosylchalcone epoxide  
 Methylamine  
 N-Methylaniline  
 Methylchalcone  
m-Methylchalcone  
m'-Methylchalcone  
p-Methylchalcone  
p'-Methylchalcone  
 $\alpha$  -Methylchalcone  
 $\beta$  -Methylchalcone  
 4'-Methyl- $\alpha$  -bromo chalcone

$\alpha$ -Methyl- $\alpha$ -carbethoxy- $\beta$ -phenyl- $\gamma$ -benzoyl-butyric ester

2-Methylcyclohexanone

3-Methylcyclohexanone

$\alpha$ -Methyl dopa

1-Methylhydrazide

Methyl . magnesium bromide

Methyl malonic ester

2-(3-(4-methyl-1-piperazinyl) propoxy-4'-methyl (and  
4'-chloro)-chalcone hydrochloride

1-(N-methyl-2-pyrryl)-3-phenyl-1-one

Methyl succinate

3,4-Methylenedioxychalcone

Metirapon

Michael addition

Michael adduct

Michael condensation

Microhydrogenation, quantitative

Miscellaneous reactions of chalcone dibromides

Molecular compounds

Molecular ion

Molecular orbital calculations

Molecular refraction

Monoperphthalic acid

Morpholine

Naphthalene analogue of chalcone

$\alpha$ -Naphthyl semicarbazide

Naringenin chalcone

Neohesperidin dihydrochalcone

Nickel

Nitration

4'-Nitrobenzoin

Nitrochalcones

o-Nitrochalcone epoxide

2-Nitrochalcone epoxide

2-Nitrochalcone thiosemicarbazone

3-Nitrochalcone

m'-Nitrochalcone

p-Nitrochalcone

4-Nitrochalcone dibromide

6-Nitrochalcone

p-Nitro-N,N-dimethylaniline

4-Nitro-1,3-diphenyl-but-1-one

Nitroethyl alcohol

Nitrohydroxychalcones

3'-Nitro-4'-hydroxy-2,3-dimethoxychalcone

3'-Nitro-4'-hydroxy-2,5-dimethoxychalcone

Nitro-isopropyl alcohol  
4-Nitro-3'-isothiocyanatochalcone  
Nitromethane  
Nitromethylchalcones  
Nitroparaffins  
o-Nitrophenols  
1-Nitropropane  
2-Nitropropane  
Nitrosophenyl ketone  
Nitrosoyl chloride  
o-Nitrotoluene  
Nomenclature  
Non-fluorescent complexes  
Nuclear bromination  
Nuclear magnetic response  
 $C^{13}$ -Nuclear magnetic resonance  
Nuclear magnetic resonance spectroscopy  
Nuclear oxidation  
Nuclear substitution  
Nucleophilic displacement  
  
Organometallic compounds  
Osmium tetroxide  
Oxazine

Oxidation

Oxidation inhibitor

Oxidative cyclisation

Oxidative phenol coupling

Oxidative phosphorylation

Oxidative rearrangement

Oxirane ring

Oxirane ring cleavage by  $\text{BF}_3$

Oxirane ring cleavage by  $\text{HCl}$

2-Oxo-4,6-diphenyl-3,6-dihydro-1,3-thiazine

$\gamma$ -oxo- $\alpha, \beta$ -diphenyl- $\alpha$ -propylene

2-Oxo-4,6-diphenyl-1,2,3,4-tetrahydropyrimidine

Oxonium salt

Oxythallation

Palladium

Palladium (II) acetate

Palladium boride,  $\text{Pd}_3\text{B}_2$

Palladium, colloidal

Papain

Paper chromatography

Pentafluorobenzene

2,3,4,5,6-Pentafluoro trans cinnamic acid

2',3,4,4',6'-Pentahydroxy chalcone-4'-glucoside

Pentanethiol

2,3,4,5,6-Pentaphenylbenzophenone

1,1,2,3,3-Pentaphenylpropanol

Perbenzoic acid

Perchloric acid

Perhydro compound

Petroleum waxes

Phellandrene

Phenol

Phenoxy fumarate

Phenoxy maleate

Phenylacetic acid (di-sodium salt)

$\beta$  -Phenyl acrylophenone

$\beta$  -Phenyl- $\beta$  (o-amino phenylmercapto) propiophenone

$\alpha$  -Phenyl- $\beta$  -benzoyl ethylene

$\beta$  -Phenyl- $\gamma$  -benzhydryl butyrophenone

2-Phenyl benzimidazole

$\beta$  -Phenyl- $\gamma$  -benzoyl- $\gamma$  -benzhydrylbutyrophenone

trans-1-Phenyl-2-benzoylcyclopropane

$\beta$  -Phenyl- $\gamma$  -benzoylbutyric acid

2- 1-Phenyl-2-benzoylethyl cyclohexan-2,6-dione

$\alpha$  -Phenyl- $\beta$  -benzoyl propionic acid

Phenyl benzyl ketone

$\beta$  -Phenyl butyrophenone

$\alpha$  -Phenylchalcone



trans-Phenylchalcone

$\beta$ -Phenyl chalcone

4-Phenylchalcone

4'-Phenylchalcone

4-Phenyl dihydrocoumarin

Phenylhydrazine

Phenylhydrazone

3-Phenyl-1-indanone

Phenyl lithium

Phenyl magnesium bromide

$\alpha$ -Phenylnitrochalcone

2-Phenyl-2-phenacyl benzyl-2,3-dihydro-1,4-benzopyrone

Phenyl potassium

Phenyl sodium

1-(Phenyl sulfinyl)-2,4-diphenyl-3-buten-2-ol

$\alpha$ -(Phenylsulphonyl) chalcone

Phenyl sulphonyl hydrazide

Phenyl styryl ketone

$\alpha$ -Phenylthiochalcone

Phenyl sulfenyl chloride

Phenyl sulfenyl methyl ester

o-Phenylene diamine

Phlorizin

Phosphoric acid

Phosphorylated esters of chalcones

Photochemical demethylation

Photochemical dimerization

Photochemical isomerization

Photochemical oxidation

Photochemistry, solid state

Photoconducting composition

Photocross linkable copolymers

cis-trans Photo-isomerization, Mechanism and kinetics

Photolysis

Photo-oxidative cleavage

Photosensitive polymeric material

Photo-thermographic emulsion

Picric acid

Pinacol

Piperidine

Piperizine

pKa

Plastics

Platinum

Platinum black

Platinum oxide

Polarization

Polarographic reduction

Polarographic reduction potential

Polyacrylates

Polyamide column chromatography  
Polychrome isomers  
Poly (dimethyl siloxane)  
Polyester film  
Poly fluorochalcons  
Polyhydroxylated chalcone  
Polymerization catalyst  
Polymethyl methacrylate  
Polymorphic forms of chalcone  
Polymorphism  
Polyolefinic polymers  
Polyphenols  
Polypropylene polymer  
Potassium amide  
Potassium borohydride  
Potassium tert. butoxide-t-butyl alcohol  
Potassium cyanide  
Potassium ferricyanide  
Potassium iodide  
Potassium isocyanide  
Potassium persulphate  
  
Prenyloxychalcone  
Preparative T.L.C.  
Promoters

β-Propoxychalcone

Protolytic equilibrium

Proton magnetic resonance

PVC resin sheets

Pyranochalcone

Pyran derivative

Pyrazolines

Pyridine

Pyridine analogue of chalcone

Pyridine-borane reagent

Pyrolysis

Pyrolytic oxidative cleavage

Pyrryl analogue of chalcone

Pyrrole

3-Pyrrole-3-aldehydechalcone

Pyrrolidine

1 (2-pyrryl)-3-aryl-prop-3-one

Pyrylium salt

Quantum chemical methods

Quinacetophenone

Quinacetophenone monomethyl ether

Quinoline

Quinoline analogue of chalcone

Radical anion

Raman spectrum

Raney nickel

Rearrangement ions

Reduced benzofuran chaloone derivative

Reduction dimers

Reductive amination

Reductive cyclisation

Reductive dehalogenation

Relative basicities of chalcones

Resacetophenone

Resacetophenone dimethyl ether

Resin

Resinification

Resorcylic chalcone

$R_f$  values of benzenoid chalcones

Ferrocene analogue of chalcones

Furyl analogue of chalcone

Pyrryl analogue of chalcone

Thienyl analogue of chalcone

Ring cyclisation

Ritter reaction

Rotation about  $C_\alpha - C_\beta$  bond

Rotational isomers

Ruthenium (II) complex

Saccharin

Salicylic acid

Salicylic acid chalcone

Schmidt reaction

Scintillators

Secondary amine-iodine complex

Selenium dioxide

Selenophene analogues of chalcone and its analogue

Semicarbazone of chalcone and its analogue

Sigma ( $\sigma$ ) constant

Silicone dielectric fluid

Silver halide emulsion

o-silylated ketenes

Skeletal rearrangement

Sodium

Sodium-alcohol

Sodium amide

Sodium azide

Sodium bisulphite

Sodium borohydride

Sodium borohydride-boron trifluoride

Sodium dithionate

Sodium enol methyl malonic ester

Sodium hydrogen sulphide

Sodium hydrogen sulphite  
Sodium-potassium dependent ATP-ase  
Sophoradin  
Spectrophotometric analysis  
Stannous chloride  
Stereochemistry  
Stereoisomeric pairs  
Stereoisomerism  
Stereoisomers  
Steric effects  
Steric hindrance  
Styrene-maleic anhydride  
N-substituted-4'-aminoalkyl-2',4-dihydroxy chalcone salt  
p-substituted benzohydride  
4-substituted chalcone  
4'-substituted chalcone  
Substituted chalcones  
 $\alpha$ -substituted chalcone  
Substituted chalcone epoxide  
  
Substituted urea  
Sulfenyl compounds  
Sulpholane  
Sulphonation  
Sulphonic acid derivative of chalcone

Sulphur

Sulphuric acid-acetic anhydride

Sulphuric acid ester of chalcone

Sulphuric acid-methanol

Sulphuric acid-nitric acid

Sweeteners

Syn conformation

Syn-s-cis-conformation

Tautomerism

Terpene

Tetrabromo-o-benzoquinone

Tetrahydrofuran

3,3',4,4'-Tetrahydroxy chalcone

2',4,4',6'-Tetrahydroxy chalcone

2',4,4',6'-Tetrahydroxy chalcone-2,  $\beta'$ -glucoside

3,2',4',6'-Tetrahydroxy-4-propoxy dihydro-4,  $\beta'$ -neo hesperodside

2',3,4,4'-Tetramethoxy chalcone epoxide

5,7,3',4'-Tetramethoxyflavanonol

Tetramethoxy eriodictyol chalcone

$\pm$  3',4',5,7-Tetra-o-methyl taxifolin

Tetraphenyl borocopper

1,2,4,5-Tetraphenylcyclohexan-1,2-diol

Tetraphenylcyclopentadienone



1,3,4,6-Tetraphenyl-3,4-dihydroxy-1,5-hexadiene

1,3,4,6-Tetraphenyl-hexan-1,6-dione

1,3,6,8-Tetraphenyl-1,8-octadione

1,1,3,3-Tetraphenyl-1-1-propanol

2,3,3,3-Tetraphenyl propyl phenyl ketone

Tetraphenyl tin

Thallic acetate

Thallic nitrate

1,3-thiazium salts

Thienyl analogue of chalcone

Thin-layer chromatography

Thioalcohols

4'-Thioalkyl chalcone

Thioaurones

Thiobarbituric acid

Thiocyanogen

$\alpha$ -Thiocyanato chalcone

Thiomicid

Thiphen analogue of chalcone

Thiophene-pyridine

Thiophenols

Thiosemicarbazone of chalcone and its analogue

Thiourea

Titanium tetrachloride

Toluene thiol

p-Tolylamine

$\beta$ -Tolychalcone

1-(-ptolyl)-2-hydroxy-3-chloro-3-phenyl-propan-1-one

2'-Tosychalcone epoxide

2'-Tosyl-6'-methoxy chalcone

Tosyl-hydrazine

Tosyl hydrazone

n- $\pi^*$  and  $\pi - \pi^*$  transitions

Transmutation

Transmission effects

Transoid conformation

Triamino guanidine salt

Tributyl tin

Trichloroacetic acid

Trifluoroperoxyacetic acid

3,4,4'-Trihydroxy-3'-carboxychalcone

2,2',4-Trihydroxychalcone

2,4,4'-Trihydroxychalcone

2',4',6'-Trihydroxychalcone

3,2',4'-Trihydroxy-4-methoxy-dihydrochalcone

Trimethoxy aluminium hydride

2',4,4'-Trimethoxychalcone (vesidryl)

4,2',4'-Trimethoxychalcone epoxide

( $\pm$ ) 4',5,7-tri-o-methyl aromaden-drin

Triphenyl aluminium

1,3,5-Triphenyl-4-benzoyl-hex-1,3-diene

1,3,5-Triphenyl-4-benzyl-1-pentene

triphenyl cadmium lithium

$\alpha, \beta, \delta$  -Triphenyl- ~~$\alpha$~~ -dimethylamino- $\delta$ -ketovaleronitrile

$\beta, \gamma, \gamma$  -Triphenyl- $\gamma$ -hydroxybutyrophenone

Triphenyl indium

Triphenyl methyl sodium

1,3,5-Triphenyl-pentan-1,5-dione

trans 1,1,3-Triphenyl-2-propen-1-ol

1,3,5-Triphenyl pyrazolines

2,4,6-Triphenylpyridine

2,4,6-Triphenyl pyrimidine

2,4,6-Triphenyl pyrylium chloride

Triphenyl thallium

Triphenyl tin lithium

Triplet mechanism

2,4,6-Trisubstituted pyridine

Triton-B

Ultraviolet absorption-filter

Ultraviolet irradiation

Ultraviolet spectra, cis-trans isomer of chalcone

$\alpha, \beta$  -Unsaturated alcohol

$\alpha, \beta$  -Unsaturated ketone

Unsaturated ketoximes

Unsaturated trimer

Uranyl chloride

Urea

Uvaretin

Vanadous salt

Veratraldehyde

Vesidryl (see 2',4,4'-trimethoxychalcone)

Willgerodt-Kindler reaction

Wilson's boric acid test

Xanthine oxidase

Xanthoangelol

X-ray crystallography

Zinc acetate

Zinc-ethanol-acetic acid

Zinc-mercury-acetic acid